Mushroom intake and risk of incident disabling dementia: the Circulatory Risk in Communities Study (CIRCS)

Shoko Aoki[1,2,3], Kazumasa Yamagishi[1,3]*, Kotatsu Maruyama[4], Ai Ikeda[5], Masanori Nagao[6], Hiroyuki Noda[7], Mitsumasa Umesawa[1,8], Mina Hayama-Terada[9], Isao Muraki[7], Chika Okada[10], Mari Tanaka[10], Rie Kishida[1,11], Tomomi Kihara[1], Midori Takada[12], Yuji Shimizu[12], Tetsuya Ohira[6], Hironori Imano[10], Tomoko Sankai[13], Takeo Okada[14], Takeshi Tanigawa[5], Akihiko Kitamura[9], Masahiko Kiyama[14] and Hiroyasu Iso[1,15]

[1]*Department of Public Health Medicine, Institute of Medicine, and Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan*
[2]*Doctoral Program in Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan*
[3]*Ibaraki Western Medical Center, Chikusei, Japan*
[4]*Department of Bioscience, Graduate School of Agriculture, Ehime University, Matsuyama, Japan*
[5]*Department of Public Health, Juntendo University, Tokyo, Japan*
[6]*Department of Epidemiology, Fukushima Medical University School of Medicine, Fukushima, Japan*
[7]*Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Suita, Japan*
[8]*Dokkyo Medical University, School of Medicine, Mibu, Japan*
[9]*Yao City Public Health Center, Yao, Japan*
[10]*Department of Public Health, Kindai University, Osakasayama, Japan*
[11]*Saw Swee Hock School of Public Health, National University of Singapore, Singapore*
[12]*Epidemiology Section, Division of Public Health, Osaka Institute of Public Health, Osaka, Japan*
[13]*Department of Public Health and Nursing, Institute of Medicine, University of Tsukuba, Tsukuba, Japan*
[14]*Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan*
[15]*Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan*

Abstract

It is uncertain whether dietary intake of mushrooms rich in dietary fibre and several antioxidants is associated with a lower risk of dementia. We sought to examine prospectively the association between mushroom intake and the risk of disabling dementia. We performed a prospective study involving 3750 people aged 40 to 64 years residing in three communities who participated in an annual cardiovascular risk survey from 1985 to 1999. Cases of incident disabling dementia were surveyed from 1999 to 2020. We calculated the hazard ratios (HR) and 95 % CI for incident total dementia according to mushroom intake among participants with or without a history of stroke. During a mean 16·0 years' follow-up in 3739 eligible participants, 670 people developed disabling dementia. For women, mushroom intake was inversely associated with the risk of total dementia and the association was confined to dementia without a history of stroke. The multivariable HR (95 % CI) for total dementia in women were 0·81 (0·62, 1·06) for mushroom intake of 0·1–14·9 g/d and 0·56 (0·42, 0·75) for mushroom intake above 15·0 g/d ($P_{\text{for trend}} = 0\cdot003$) compared with no intake. The corresponding HR (95 % CI) for dementia without a history of stroke were 0·66 (0·47, 0·93) and 0·55 (0·38, 0·79) ($P_{\text{for trend}} = 0\cdot01$). In men, no associations were observed between mushroom intake and the risk of disabling dementia. Among Japanese women, dietary mushroom intake was associated with a lower risk of disabling dementia.

Keywords: **Mushroom: Dementia: General population: Follow-up study**

One of the characteristics of the Japanese diet is a high consumption of mushrooms[1]. Mushrooms are rich in dietary fibre, the intake of which has been associated with a lower risk of dementia[2]. However, so far, only one Japanese cohort study has reported an association between mushroom intake and the risk of dementia, and they found an inverse association only among women[3]. In addition, several cross-sectional studies reported that mushroom intake was associated with improved cognitive performance[4–7]. However, the reasons for the sex-related discrepancy of association remain unclear. Although different types of dementia (including Alzheimer's disease and vascular dementia) are assumed to have different mechanisms and risk factors, analyses based on a classification of dementia types have not yet been conducted.

The Circulatory Risk in Communities Study (CIRCS) conducted a 24-h recall dietary survey in several communities in Japan and has been followed up to assess the risk of incident dementia and stroke. In the present study, we sought to investigate whether mushroom intake is inversely associated with the risks of incident disabling dementia and dementia with/without a history of stroke among Japanese men and women.

Methods

Design and study population

CIRCS is an ongoing dynamic community-based prospective study involving five communities in Japan. Details of the CIRCS protocol have been described elsewhere[8]. In the present study, cases of incident disabling dementia were surveyed in three of those five communities: Ikawa (a rural town in Akita Prefecture in northeastern Japan), Kyowa (a rural town in Ibaraki Prefecture in mid-eastern Japan) and Yao (a city in Osaka Prefecture in mid-western Japan).

We performed a prospective study involving 3750 people aged 40–64 years who lived in these three communities and participated in an annual cardiovascular risk survey from 1985 to 1999. Cases of incident disabling dementia were surveyed from 1999 to 2020 (except for the period from April 2005 to April 2008, when the data were unavailable) in Kyowa, from 1999 to 2019 in Ikawa and from 2006 to 2019 in Yao. We did not collect information on the history of dementia during the baseline survey when the participants were generally healthy and could answer questions in the dietary interview. Instead, we excluded those who developed disabling dementia within 5 years of the dietary survey (*n* 2). Persons with invalid dietary data were also excluded (*n* 9). This resulted in a total study population of 3739 people (1650 men and 2089 women).

Dietary survey

We conducted a 24-h recall dietary survey which investigated how much the participants had eaten during the 24 h prior to the interview conducted by well-trained dietitians. We recorded the foods consumed and their amounts and then calculated the energy intake and the nutrient intake on the basis of the Standard Tables of Food Composition in Japan, 7th revised edition[9]. The major foods recorded as mushrooms were *shiitake* (Lentinula edodes), *shimeji* (Hypsizygus tessulatus), *enokitake* (Flammulina filiformis) and *nameko* (Pholiota microspora) mushrooms.

Other risk factors

The measurement of potential risk factors for dementia was conducted at the time of the dietary survey, and these factors have been described in a prior publication[10]. The participants rested for at least 5 min and then had their arterial systolic pressure and fifth-phase diastolic blood pressure measured. Well-trained study physicians or nurses conducted blood pressure measurements using standard mercury sphygmomanometers on the right arm of the participants. The physician conducted the measurement again when the first reading showed a systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg. In such cases, the second reading was used in the analysis; otherwise, the first reading was used. We measured the height and weight of participants wearing light clothing and with their shoes off and calculated the BMI (weight in kilograms divided by height in metres squared). We collected information on smoking status (never, former or current), number of cigarettes smoked per d, alcohol drinking status (never, former or current), the amount of alcohol consumption per d, prescriptions for antihypertensives, cholesterol-lowering and diabetes drugs, and history of a stroke through face-to-face interviews. We measured serum glucose and total cholesterol without a fasting requirement. The definition of diabetes mellitus was a fasting serum glucose level greater than or equal to 126 mg/dl or a non-fasting serum glucose level greater than or equal to 200 mg/dl and/or being on medication for diabetes.

Definition of disabling dementia

The outcome of the present study was dementia requiring care ('disabling dementia'), which was based on the National Long-Term Care Insurance System. This insurance system is compulsory for all individuals aged 40 years or more in Japan[11]. Physicians identified disabling dementia according to the physicians' manual issued by the Ministry of Health, Labour and Welfare of Japan[12]. We regarded disabling dementia as the following two conditions: (1) certified for disability under the long-term care insurance programme and (2) with a grade of activities of daily living related to dementia above the class of IIa (i.e. some symptoms/behaviours or communication difficulties that interfere with daily life and need someone's assistance to live by themselves)[13]. These criteria have been previously validated against the diagnosis by certified psychiatrists with high specificity (96 %) and moderate sensitivity (73 %)[14], and the grade of activities of daily living related to dementia was found to be highly correlated with the Mini-Mental State Examination score[15]. We did not possess the data on the specific types of dementia (i.e. Alzheimer's disease and vascular dementia). Instead, we classified disabling dementia into two subtypes: with or without a history of stroke based on a systematic stroke registration during the follow-up period for disabling dementia and the self-reported history of stroke at the time of the dietary survey. The definition of stroke in our systematic registration was a rapid-onset focal neurological

disorder persisting for more than 24 h or until death. In the present study, we identified 90 % of stroke occurrences using standardised criteria based on computed tomography or MRI[16], while the remainder were identified using previously reported clinical criteria for diagnosis without imaging[17,18]. Due to the availability of stroke registry data, the stroke subtype analysis was conducted using the follow-up data until 31 December 2015 for Kyowa, and until 31 December 2018 for Ikawa and Yao.

Statistical analysis

We classified participants into three groups according to mushroom intake per d: no intake (0 g/d), intake below the median (0·1–14·9 g/d) and intake above the median (≥ 15·0 g/d) on the basis of the dietary survey conducted from 1985 to 1999. Age- and sex-adjusted means and percentages of characteristics of participants at the time of the dietary survey were compared between groups. Follow-up started from 1999 (2006 for Yao) and ended at the time of diagnosis of incident dementia, move out to a different community, death or end of follow-up, whichever came first. We calculated hazard ratios (HR) and 95 % CI for incident total dementia and dementia with/without a history of stroke for the two groups of participants with some mushroom intake (mushroom intake between 0·1 and 14·9 g/d, and mushroom intake greater than 15·0 g/d) compared with the group with no mushroom intake using Cox proportional hazard models sex-specifically. The proportional hazards assumption was tested using the interaction term of time by mushroom intake and was not violated for each outcome. We adjusted for age (continuous) and nested by communities in model 1. We further adjusted for energy intake (continuous), smoking status, drinking status, intakes of vegetables (quartile), fruits (quartile), fish (quartile), meat (quartile) and sodium (quartile) in model 2. The soluble fibre intake (quartile) was further adjusted in model 3, and the insoluble fibre intake (quartile) in model 4. We evaluated multiplicative interaction between men and women. The statistical significance of multiplicative interactions of HR were calculated using the Wald test. Analyses were conducted using SAS 9.4 (SAS Institute). All probability values for the statistical tests were two-tailed, and probability values below 0·05 were considered significant.

Results

During 16·0 years of average follow-up in 3739 participants, a total of 670 people (260 men and 410 women) developed disabling dementia. The incidence rates per 1000 person-years were 10·2 in men and 12·0 in women, respectively.

Table 1 shows the age- and sex-adjusted baseline characteristics according to mushroom intake. The proportion of women, being prescribed cholesterol-lowering medication, the mean value of diastolic blood pressure, and intakes of total fat, protein, total fibre, vegetables, meat and sodium were positively correlated with mushroom intake (Table 1).

For women, mushroom intake was inversely associated with the risk of total dementia and dementia without a history of stroke, but not with dementia with a history of stroke (Table 2). Among women, the multivariable HR (95 % CI) in model 2 for

Table 1. Characteristics of participants according to mushrooms intake at dietary surveys

	Mushrooms intake (g/d)			
	0	0·1–14·9	≥ 15	$P_{for\ trend}$
Number	2560	528	651	
Age (year*)	51·4	51·2	50·9	0·11
Women (%†)	51·7	65·0	65·0	< 0·001
BMI (kg/m²)	23·8	23·8	23·7	0·68
Current smoker (%)	30·0	22·2	20·9	0·31
Current drinker (%)	41·4	33·7	35·5	0·22
Systolic blood pressure (mmHg)	130	131	131	0·18
Diastolic blood pressure (mmHg)	81·1	81·3	81·9	0·02
Antihypertensive medication (%)	12·5	11·0	13·1	0·44
Diabetes mellitus (%)	4·9	4·7	4·1	0·90
History of stroke (%)	1·0	0·8	1·2	0·61
Serum total cholesterol (md/dl)	199	202	202	0·43
Cholesterol-lowering medication (%)	1·9	1·7	3·5	0·03
Energy (kcal/d)	1989	1948	1950	0·23
Carbohydrate (g/d)	291	281	278	0·49
Total fat (g/d)	46·5	46·5	49·1	0·0009
Protein (g/d)	69·9	71·0	72·0	< 0·001
Total fibre (g/d)	14·3	15·4	16·9	< 0·001
Soluble fibre (g/d)	3·0	3·1	3·5	< 0·001
Insoluble fibre (g/d)	10·5	11·5	12·7	< 0·001
Intakes of vegetables (g/d)	267	267	318	< 0·001
Intakes of fruit (g/d)	142	139	161	0·07
Intakes of fish (g/d)	97·7	97·7	91·3	0·35
Intakes of meat (g/d)	46·5	49·4	56·4	< 0·001
Intakes of Na (mg/d)	4522	4664	4764	< 0·001
Intakes of *shiitake* (g/d)	0	3·4	13·4	< 0·001
Intakes of *shimeji* (g/d)	0	0·9	6·3	< 0·001
Intakes of *enokitake* (g/d)	0	0·6	7·4	< 0·001
Intakes of *nameko* (g/d)	0	0·5	2·2	< 0·001
Intakes of vitamin D (mg/d)	10	9·5	9·2	< 0·001

Otherwise adjusted for age and sex.
* Adjusted for sex.
† Adjusted for age.

total dementia for those with mushroom intake between 0·1 and 14·9 g/d and those with mushroom intake greater than or equal to 15·0 g/d were 0·81 (0·62, 1·06) and 0·56 (0·42, 0·75) ($P_{for\ trend}$ = 0·003), respectively, while the multivariable HR (95 % CI) for dementia without a history of stroke were 0·66 (0·47, 0·93) and 0·55 (0·38, 0·79) ($P_{for\ trend}$ = 0·01), respectively, compared with those with no mushroom intake. The multivariable HR (95 % CI) per 10 g/d increment of mushroom intake were 0·89 (0·82, 0·96) for total dementia and 0·88 (0·80, 0·98) for dementia without a history of stroke. However, we did not observe any associations between mushroom intake and the risk of disabling dementia in men. Further adjustment for intakes of soluble and insoluble fibres slightly attenuated the associations of mushroom intake with the risk of total dementia and the risk of dementia without a history of stroke in women, but we still observed significant associations. We adjusted further for hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or taking antihypertensive medication), diabetes mellitus (fasting glucose ≥ 126 mg/dl or non-fasting glucose ≥ 200 mg/dl and/or taking medication) and obesity (BMI ≥ 25 kg/m²) which could mediate the mushroom–dementia association, but the results did not change. The multivariable HR of total dementia for mushroom intake between 0·1 and 14·9 g/d and mushroom intake greater than or equal to 15·0 g/d were 0·85 (0·65, 1·12) and 0·58 (0·43, 0·78),

Table 2. Multivariable hazard ratios and 95 % CI of incident dementia according to mushrooms intake

Men		Hazard ratios	95 % CI	Hazard ratios	95 % CI		
Mushrooms intake (g/d)	0	0·1–15·0		> 15·0		$P_{\text{for trend}}$	$P_{\text{for interaction}}$ by sex
Number of subjects	1237	185		228			
Total dementia							
Person-years	19 038	2825		3688			
Number of cases	201	24		35			
Incidence rate per 1000 person-years	10·6	8·4		9·5			
Model 1	1·00	0·97	0·63, 1·48	1·12	0·78, 1·61	0·44	0·005
Model 2	1·00	1·29	0·59, 2·82	0·84	0·38, 1·88	0·29	0·006
Model 3	1·00	1·12	0·73, 1·74	1·21	0·84, 1·76	0·25	0·006
Model 4	1·00	1·13	0·73, 1·74	1·20	0·82, 1·75	0·31	0·005
Dementia without a history of stroke							
Person-years	17 127	2533		3320			
Number of cases	115	12		21			
Incidence rate per 1000 person-years	6·7	4·7		6·3			
Model 1	1·00	0·85	0·47, 1·55	1·28	0·80, 2·04	0·25	0·007
Model 2	1·00	1·09	0·59, 2·03	1·45	0·90, 2·36	0·12	0·006
Model 3	1·00	1·10	0·59, 2·04	1·49	0·92, 2·42	0·09	0·006
Model 4	1·00	1·09	0·58, 2·03	1·47	0·89, 2·41	0·12	0·005
Dementia with a history of stroke							
Person-years	17 127	2533		3320			
Number of cases	54	8		7			
Incidence rate per 1000 person-years	3·2	3·2		2·1			
Model 1	1·00	1·20	0·57, 2·54	0·80	0·36, 1·77	0·88	0·31
Model 2	1·00	1·14	0·53, 2·44	0·86	0·39, 1·91	0·70	0·35
Model 3	1·00	1·29	0·59, 2·82	0·86	0·38, 1·92	0·89	0·34
Model 4	1·00	1·30	0·60, 2·84	0·86	0·38, 1·95	0·62	0·34

Women		Hazard ratios	95 % CI	Hazard ratios	95 % CI	
Mushrooms intake (g/d)	0	0·1–15·0		> 15·0		$P_{\text{for trend}}$
Number of subjects	1323	343		423		
Total dementia						
Person-years	21 260	5600		7270		
Number of cases	280	72		58		
Incidence rate per 1000 person-years	13·1	12·9		8·0		
Model 1	1·00	0·81	0·62, 1·05	0·55	0·41, 0·73	0·002
Model 2	1·00	0·81	0·62, 1·06	0·56	0·42, 0·75	0·003
Model 3	1·00	0·83	0·63, 1·08	0·59	0·44, 0·78	0·007
Model 4	1·00	0·86	0·66, 1·13	0·60	0·45, 0·81	0·01
Dementia without a history of stroke						
Person-years	19 063	5007		6416		
Number of cases	191	41		37		
Incidence rate per 1000 person-years	10·0	8·2		5·8		
Model 1	1·00	0·67	0·48, 0·94	0·55	0·39, 0·78	0·01
Model 2	1·00	0·66	0·47, 0·93	0·55	0·38, 0·79	0·01
Model 3	1·00	0·66	0·47, 0·93	0·57	0·40, 0·82	0·03
Model 4	1·00	0·70	0·49, 0·99	0·60	0·41, 0·86	0·05
Dementia with a history of stroke						
Person-years	19 063	5007		6416		
Number of cases	28	9		7		
Incidence rate per 1000 person-years	1·5	1·8		1·1		
Model 1	1·00	1·14	0·54, 2·41	0·71	0·31, 1·63	0·27
Model 2	1·00	1·15	0·54, 2·48	0·86	0·37, 2·01	0·46
Model 3	1·00	1·22	0·56, 2·64	0·94	0·40, 2·20	0·58
Model 4	1·00	1·32	0·60, 2·88	0·91	0·38, 2·18	0·50

Model 1: Adjusted for age and energy, and stratified by area.
Model 2: Multivariable model adjusted further for smoking status, drinking status, intakes of vegetables, fruits, fish and meat.
Model 3: Multivariable model adjusted further for variables in model 2 and soluble fibre.
Model 4: Multivariable model adjusted further for variables in model 2 and insoluble fibre.

respectively, in women compared with no mushroom intake ($P_{\text{for trend}} = 0.006$).

Since the data regarding registration of dementia diagnosis between 2005 and 2008 in Kyowa were unavailable, we performed a sensitivity analysis starting follow-up from 2009 in order to reduce the possibility of reverse causation. The results did not change essentially (online Supplementary Table 1). Of

note, when we excluded the participants who had had a history of stroke, the results did not change substantially. The multivariable HR of total dementia for mushroom intake between 0·1 and 14·9 g/d and mushroom intake greater than or equal to 15·0 g/d were 0·82 (0·63, 1·07) and 0·57 (0·43, 0·77), respectively, in women compared with no mushroom intake ($P_{\text{for trend}} = 0.005$). It was also possible that mushroom

consumption varied by season, but the results were similar when the analysis was conducted separately for each of the four seasons, although they were not always statistically significant probably because the numbers of participants were limited (data not shown).

Discussion

We found an inverse association between mushroom intake and the risk of incident disabling dementia only in women. The association was confined to dementia without a history of stroke.

This sex-related discrepancy of association was consistent with a previous study. This was a prospective study involving 13 230 Japanese participants aged 65 years or above with a 5·7-year follow-up, which showed an inverse association between mushroom intake and the risk of dementia in women but not in men. The multivariable HR (95 % CI) for persons with a mushroom intake of 1–2 times/week and a mushroom intake greater than or equal to 3 times/week were 1·15 (0·92, 1·43) and 0·97 (0·76, 1·24) ($P_{for\ trend}$ = 0·83), respectively, in men, and 0·80 (0·66, 0·98) and 0·68 (0·55, 0·85) ($P_{for\ trend}$ < 0·01), respectively, in women, compared with those with a mushroom intake less than 1 time/week[3].

No other cohort study has examined the association between mushroom intake and the risk of dementia. A randomised control study of thirty Japanese aged 50–80 years, which divided participants into two 15-person groups, showed that oral administration of four 250 mg tablets containing 96 % of *yamabushitake* mushroom (Hericium erinaceus) dry powder three times a day for 16 weeks increased scores on the cognitive function scale compared with the placebo group (P < 0·001)[4]. A cross-sectional study involving 663 people aged 60 years or above in Singapore showed that mushroom consumption was associated with a lower prevalence of mild cognitive impairment. The multivariable OR (95 % CI) for mild cognitive impairment in those with mushroom consumption greater than two portions per week was 0·43 (0·23, 0·78) compared with those with mushroom consumption of less than one portion per week ($P_{for\ trend}$ = 0·006)[5]. Another cross-sectional study of 2840 people aged 60 years or more in the USA reported that greater mushroom intake was associated with higher scores on cognitive performance tests evaluating new verbal learning, immediate and delayed memory, verbal semantic fluency, attention, and processing speed[7]. Yet another cross-sectional study of 2031 people aged 70–74 years in Norway reported a significant association between a high mushroom intake (> 10th percentile or more) and better cognitive performance, including episodic memory, executive function, perceptual speed, visuo-spatial skills, an improved score on a modified version of the Mini-Mental State Examination and enhanced access to semantic memory[7]. However, the above-mentioned four studies did not show sex-specific results.

The potential effects of dietary fibre contained in mushrooms are involved in the pathophysiology of cognitive decline and dementia. The CIRCS previously showed that fibre intake, especially soluble fibre intake, was inversely associated with the risk of disabling dementia[2]. An animal study showed that the administration of soluble fibre changed the gut microbiome, which contributed to the production of butyrate, acetate, and total SCFA in the gut and to the prevention of inflammation of microglia[19]. Dietary fibre-deficient mice presented decreased *Bacteroidetes* and increased *Proteobacteria* in the gut and developed cognitive impairment, including decline of spatial memory and temporal order memory, as well as disabilities in daily living performance[20]. However, we observed a similar association between mushroom intake and the risk of disabling dementia even after further adjusting for soluble and insoluble fibre intake. Therefore, some nutrients other than dietary fibre such as vitamin B, vitamin D, polyphenol and ergothioneine could contribute to this association. It has been reported that accumulation of amyloid led to neural alterations in young and middle-aged adults[21], and that antioxidants obtained from foods may slow the neuronal damage related to amyloid β-peptide-induced oxidative stress[22]. Diet patterns containing anti-inflammatory nutrients such as vitamin B, vitamin D_3 and polyphenol decrease the levels of pro-inflammatory prostaglandins and eicosanoids and could counteract Alzheimer's disease pathologies[23]. Ergothioneine is an amino acid with potent antioxidant activity produced by fungi and actinobacteria[24]. An animal study reported that mice orally fed ergothioneine showed improved memory and learning abilities compared with the controls[25]. A human study reported that plasma levels of ergothioneine were lower in patients with mild cognitive impairment than age-matched controls without cognitive impairment[26]. These studies support our findings that mushroom intake was associated with the risk of dementia without a history of stroke (which is likely to be Alzheimer's disease), but not with the risk of dementia with a history of stroke (which is likely to be vascular dementia). However, in the present study, we calculated the HR for the risk of disabling dementia adjusted for vitamin B_1, vitamin B_2, niacin, vitamin B_6, folate, vitamin D, and vitamin K, respectively, but the results did not change. Since we did not collect information on antioxidant nutrition including polyphenol and ergothioneine, it remains unclear which specific nutrition factor contributed to the association between mushroom intake and the risk of disabling dementia.

We found the association between mushroom intake and incident disabling dementia only in women. The reason for the difference between men and women is uncertain, but the sex-dependent antioxidant metabolism in the brain affected by Alzheimer's disease may be involved; the levels of 4-hydroxynonenal (a marker of oxidative damage) were reported to be higher in female Alzheimer's disease patients than in male patients[27], which may reflect a higher susceptibility against oxidative stress than that of men. As mentioned above, mushrooms contain several antioxidant nutrients, which could protect against oxidative stress and prevent dementia more effectively in women. Although it is unclear whether mushroom intake affects sex hormone production in humans, an animal study reported that adenosine contained in mushrooms contributed to increased testosterone production[28]. A meta-analysis showed that a low testosterone level was associated with a higher risk of Alzheimer's disease[29]. On the other hand, a randomised control study involving 788 men aged 65 years or more reported that 1-year testosterone treatment did not improve cognitive

impairment[30]. Testosterone level may be a useful biomarker for dementia, but increasing production of testosterone may not contribute to the risk of dementia. As for our study, we did not find any mushroom–dementia association in men.

The strengths of this study are that participants were relatively young (59·7 years of age on average) community-dwelling people, in contrast to a prior study (aged 65 years or more)[3] allowing us to examine the association of eating habits in midlife with the risk of dementia in later life, and that the target group consisted of members of the Japanese general population, who commonly consume mushrooms. We were also able to secure a long follow-up period (24·1 years on average).

Several limitations should be noted. First, we did not survey the socio-economic status of participants, which could be a residual confounding factor. National surveys of Japanese representative population samples have showed that mushroom intake was positively correlated with household income in 2014[31] and with household expenditure between 2003 and 2007[32]. Second, we collected diet information based on a 24-h recall dietary survey, so it is likely that misclassification of dietary intake occurred. However, it is unlikely that participants who rarely ate mushrooms would happen to eat them on the day of the survey. In contrast, it is possible that a participant who occasionally ate mushrooms happened not to eat them on the day of the survey. When we collapsed those with mushroom intake between 0·1 and 14·9 g/d and those with mushroom intake greater than or equal to 15·0 g/d into one group, the multivariable HR of disabling dementia for '0·1 g/day or more intake' *versus* 'no intake' were 0·68 (0·55, 0·84) for total dementia and 0·60 (0·46, 0·79) for dementia without a history of stroke in women. We did not observe any associations between mushroom intake and risk of disabling dementia in men. Third, lifestyle changes including mushroom intake might have occurred during the follow-up period. In a subsample of participants, we examined the repeatability of mushroom intake among those who completed the dietary survey twice or more at intervals 10 (±3)-year apart (*n* 201). The 10 (±3)-year repeatability of mushroom intake was as follows: among these 201 participants, 147 were classified as having 'no mushroom intake' (0 g/d) in the first survey, and 94 (64 %) of these 147 participants were classified as having 'no mushroom intake' (0 g/d) in the second survey (kappa statistic = 0·11). Fourth, we did not have data on dementia types. We assumed that dementia with a history of stroke was likely to be vascular dementia and that dementia without a history of stroke was likely to be Alzheimer's disease. Last, we did not collect data on the history of dementia at the baseline survey. Instead, we excluded those who developed disabling dementia within 5 years of the baseline survey. Furthermore, since cases of incident dementia were not registered from 2005 to 2008 in Kyowa and from 1999 to 2005 in Yao, we performed a sensitivity analysis starting the follow-up from 2009, and we generally observed the same results (online Supplementary Table 1).

In conclusion, mushroom intake was associated with a lower risk of incident disabling dementia, especially dementia without a history of stroke, among Japanese women.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452400014X

References

1. Nanri A, Shimazu T, Ishihara J, *et al.* (2012) Reproducibility and validity of dietary patterns assessed by a food frequency questionnaire used in the 5-year follow-up survey of the Japan public health center-based prospective study. *J Epidemiol* **22**, 205–215.
2. Yamagishi K, Maruyama K, Ikeda A, *et al.* (2022) Dietary fiber intake and risk of incident disabling dementia: the circulatory risk in communities study. *Nutr Neurosci* **26**, 148–155.
3. Zhang S, Tomata Y, Sugiyama K, *et al.* (2017) Mushroom consumption and incident dementia in elderly Japanese: the Ohsaki Cohort 2006 Study. *J Am Geriatr Soc* **65**, 1462–1469.
4. Mori K, Inatomi S, Ouchi K, *et al.* (2009) Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. *Phytother Res* **23**, 367–372.
5. Feng L, Cheah IK-M, Ng MM-X, *et al.* (2019) The association between mushroom consumption and mild cognitive impairment: a community-based cross-sectional study in Singapore. *J Alzheimers Dis* **68**, 197–203.
6. Ba DM, Gao X, Al-Shaar L, *et al.* (2022) Mushroom intake and cognitive performance among US older adults: the National Health and Nutrition Examination Survey, 2011–2014. *Br J Nutr* **128**, 2241–2248.

7. Nurk E, Refsum H, Drevon CA, et al. (2010) Cognitive performance among the elderly in relation to the intake of plant foods. The Hordaland Health Study. Br J Nutr 104, 1190–1201.

8. Yamagishi K, Muraki I, Kubota Y, et al. (2019) The Circulatory Risk in Communities Study (CIRCS): a long-term epidemiological study for lifestyle-related disease among Japanese men and women living in communities. J Epidemiol 29, 83–91.

9. Ministry of Education, Culture, Sports, Science and Technology (2015) Standard Tables of Food Composition in Japan, 7th revised ed. Tokyo: Ministry of Education, Culture, Sports, Science and Technology.

10. Aoki S, Yamagishi K, Maruyama K, et al. (2021) Dietary intake of tocopherols and risk of incident disabling dementia. Sci Rep 11, 16429.

11. Tamiya N, Noguchi H, Nishi A, et al. (2011) Population ageing and wellbeing: lessons from Japan's long-term care insurance policy. Lancet 378, 1183–1192.

12. Health and Welfare Bureau for the Elderly M of H labour and Welfare (1993) Standardized Assessment Manual for the Grade of Activity Daily Living Related to Dementia among Elderly with Dementia. Tokyo: Ministry of Labour & Employment.

13. Ikeda A, Yamagishi K, Tanigawa T, et al. (2008) Cigarette smoking and risk of disabling dementia in a Japanese rural community: a nested case-control study. Cerebrovasc Dis 25, 324–331.

14. Noda H, Yamagishi K, Ikeda A, et al. (2018) Identification of dementia using standard clinical assessments by primary care physicians in Japan. Geriatr Gerontol Int 18, 738–744.

15. Hisano S (2009) The relationship between Revised Hasegawa Dementia Scale (HDS-R), Mini-Mental State Examination (MMSE) and bed-fast scale, dementia scale. Jpn J Geriatr Psychiatr 20, 883–891.

16. Iso H, Rexrode K, Hennekens CH, et al. (2000) Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. Ann Epidemiol 10, 81–87.

17. Shimamoto T, Komachi Y, Inada H, et al. (1989) Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation 79, 503–515.

18. Imano H, Iso H, Kiyama M, et al. (2012) Non-fasting blood glucose and risk of incident coronary heart disease in middle-aged general population: the Circulatory Risk in Communities Study (CIRCS). Prev Med (Baltim) 55, 603–607.

19. Matt SM, Allen JM, Lawson MA, et al. (2018) Butyrate and dietary soluble fiber improve neuroinflammation associated with aging in mice. Front Immunol 9, 1832.

20. Shi H, Ge X, Ma X, et al. (2021) A fiber-deprived diet causes cognitive impairment and hippocampal microglia-mediated synaptic loss through the gut microbiota and metabolites. Microbiome 9, 223.

21. Kennedy KM, Rodrigue KM, Devous MD, et al. (2012) Effects of beta-amyloid accumulation on neural function during encoding across the adult lifespan. Neuroimage 62, 1–8.

22. Butterfield D, Castegna A, Pocernich C, et al. (2002) Nutritional approaches to combat oxidative stress in Alzheimer's disease. J Nutr Biochem 13, 444.

23. Szczechowiak K, Diniz BS & Leszek J (2019) Diet and Alzheimer's dementia - nutritional approach to modulate inflammation. Pharmacol Biochem Behav 184, 172743.

24. Borodina I, Kenny LC, McCarthy CM, et al. (2020) The biology of ergothioneine, an antioxidant nutraceutical. Nutr Res Rev 33, 190–217.

25. Yang N-C, Lin H-C, Wu J-H, et al. (2012) Ergothioneine protects against neuronal injury induced by β-amyloid in mice. Food Chem Toxicol 50, 3902–3911.

26. Cheah IK, Feng L, Tang RMY, et al. (2016) Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline; a risk factor for neurodegeneration? Biochem Biophys Res Commun 478, 162–167.

27. Schuessel K, Leutner S, Cairns NJ, et al. (2004) Impact of gender on upregulation of antioxidant defence mechanisms in Alzheimer's disease brain. J Neural Transm (Vienna) 111, 1167–1182.

28. Iguchi K, Nagashima K, Mochizuki J, et al. (2023) Enokitake mushroom and its active component, adenosine, which restores testosterone production in impaired and fatigued mouse models. Nutrients 15, 2142.

29. Lv W, Du N, Liu Y, et al. (2016) Low testosterone level and risk of Alzheimer's Disease in the elderly men: a systematic review and meta-analysis. Mol Neurobiol 53, 2679–2684.

30. Yeap BB & Flicker L (2022) Testosterone, cognitive decline and dementia in ageing men. Rev Endocr Metab Disord 23, 1243–1257.

31. Ministry of Health Labour and Welfare (2016) The National Health and Nutrition Survey in Japan. https://www.mhlw.go.jp/bunya/kenkou/eiyou/h26-houkoku.html (accessed March 2022).

32. Nishi N, Horikawa C & Murayama N (2017) Characteristics of food group intake by household income in the National Health and Nutrition Survey, Japan. Asia Pac J Clin Nutr 26, 156–159.

British Journal of Nutrition