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Dietary fiber intake and risk of incident disabling dementia: the Circulatory Risk in Communities Study

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ABSTRACT

Objectives: It has been hypothesized that dietary fiber intake has a beneficial impact on prevention of dementia, but the epidemiological evidence is scant. We sought to examine whether dietary fiber intake is inversely associated with risk of dementia requiring care under the national insurance (disabling dementia).

Methods: The study setting was the Circulatory Risk in Communities Study, involving 3739 Japanese individuals aged 40–64 years at the dietary surveys (1985–99). Dietary fiber intake was estimated using the 24-hour dietary recall method. Incident disabling dementia was followed up from 1999 through 2020. Disabling dementia was further classified into that with or without a history of stroke. Hazard ratios of disabling dementia according to quartiles of total, soluble, and insoluble fiber intake were calculated using the Cox proportional hazards model.

Results: During a median 19.7-year follow-up, a total of 670 cases of disabling dementia developed. Dietary fiber intake was inversely associated with risk of dementia: the multivariate hazards ratios (95% confidence intervals) were 0.83 (0.67–1.04), 0.81 (0.65–1.02), and 0.74 (0.57–0.96) for individuals with the second, third, and highest quartiles of dietary fiber intake, respectively, as compared with the lowest quartile (P for trend = 0.03). The inverse association was more evident for soluble fiber intake and was confined to dementia without a history of stroke. As for fiber-containing foods, potatoes, but not vegetables or fruits, showed a similar association.

Conclusions: Dietary fiber intake, especially soluble fiber, was inversely associated with risk of disabling dementia in a general Japanese population.

KEYWORDS


Dietary fiber; diet; nutrition; cognitive dysfunction; disabling dementia; epidemiology; follow-up study; cohort study


Introduction

Dietary fiber is a component that reaches the large intestine without being affected by digestive enzymes in the small intestine but is thought to affect the bacterial flora in the large intestine [1] and may lead to health benefits [2]. Recently, brain-gut interaction has received attention in terms of the development of dementia [3]. The concept of brain-gut interaction emerged from the idea that the central nervous system communicates

bidirectionally with the gastrointestinal tract, suggesting that the gut microbiome may influence brain plasticity and cognitive function [4]. For example, a cross-sectional study of 128 Japanese patients who visited a memory clinic showed that the number of *Bacteroides* species was lower among patients with dementia than among those without it [5].

A soluble high-fiber food or diet enhanced the abundance of the *Bacteroides* species in mice [6]. Another mice study showed that a soluble high-fiber diet

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attenuated neuroinflammation associated with ageing via butyrate-induced gut bacteria [7], whilst insoluble fiber was not reported to have such a neuroprotective effect. Most insoluble fibers have not been recognized as prebiotics [1], but some animal studies have suggested that insoluble fibers were involved in the regulation of the gut microbiome [8].

In this context, we sought to test the hypothesis that dietary intake of fiber, especially soluble fiber, is associated with a reduced risk of dementia. As secondary analyses, we classified dementia into that with a history of stroke and that without it and hypothesized an inverse association between fiber intake and risks of both types of dementia via the antiatherosclerotic and neuroprotective effects of dietary fiber. We previously reported an inverse association between intake of beans, a fiber-containing food, and risk of disabling dementia [9]. We here extended the analyses to dietary intakes of total, soluble, and insoluble fibers and other fiber-containing foods (i.e. potatoes, vegetables, and fruits) in relation to risk of disabling dementia. We distinguished potatoes from vegetables because the composition of starch in potatoes and vegetables is quite different, potatoes are considered as a different category from vegetables in Japanese food culture, and potatoes are classified separately from vegetables in the Standard Tables of Food Composition in Japan.

Methods

Study cohort

The Circulatory Risk in Communities Study (CIRCS) is an ongoing dynamic community cohort study involving five communities in Japan. Details of the CIRCS protocol have been described elsewhere [10]. In the present study, we included three communities, Ikawa, Yao, and Kyowa, where disabling dementia surveillance is being conducted.

A total of 9992 people aged 40–69 years living in these three communities participated in the annual health checkups between 1985 and 1999. Of these, 38% of the participants, usually systematically sampled, underwent the dietary surveys. We determined the risk set as 3750 people who first participated in the dietary surveys from 1985 to 1999. They were followed up to confirm incident dementia from 1999 through 2020 (except for from April 2005 to April 2008, for which period the data were unavailable) in Kyowa; from 1999 through 2019 in Ikawa; and from 2006 through 2019 in Yao (Figure 1).

The participants were primarily healthy at the time of the dietary surveys, and we did not ask about history of

dementia in the dietary surveys. Instead, we excluded persons who participated in the dietary survey at least five years before receiving a dementia diagnosis ($n = 2$ excluded) to minimize the possibility of reverse causation. We further excluded nine persons with invalid dietary data. In the end, a total of 3739 participants were involved in this study.

Disabling dementia

From the perspective of preventing dementia that requires care, we determined the outcome of this study as dementia that required care (disabling dementia) under the National Long-Term Care Insurance System, which is a national compulsory insurance for all individuals aged 40 years or older in Japan. The criteria for disabling dementia were the same as those of our previous study [11]; that is, onset of disabling dementia was defined as the first time the following two conditions were met: (1) ‘the level of care require’ being ≥ 1 (requiring assistance with some or all daily activities for six months or more owing to physical or mental disabilities) and (2) ‘the grade of activities of daily living related to dementia’ being $\geq \text{II}$ (grade II is equivalent to moderate dementia-related behavioral disturbance and cognitive impairment with slight dependence) diagnosed by attending physicians under the National Long-Term Care Insurance System. The validation of the criteria was previously confirmed by comparison with the clinical diagnoses of neuropsychiatrists with high specificity (96%) and with moderate sensitivity (73%) [12]. For the subtype analyses, we further classified the dementia cases into those with or without a history of stroke on the basis of a systematic stroke registration described in our previous study [13], as well as of self-reports provided at the time of the dietary surveys. For the subtype analyses, the follow-up ended on 31 December 2015 for Kyowa and on 31 December 2018 for Ikawa and Yao owing to the availability of the stroke registry data.

Dietary surveys

An interview to administer the 24-hour dietary recall for one day was conducted by trained dietitians, who asked what and how much the participants had eaten during the 24 hours before the interview. In the interview, actualized food models, pictures of food materials and dishes, and/or real foods and dishes such as rice and miso soup were shown to the participant to help him/her with recall of food intake. On the basis of the interview, the foods consumed and their amount were coded, and the intake of each nutrient (including total, soluble,

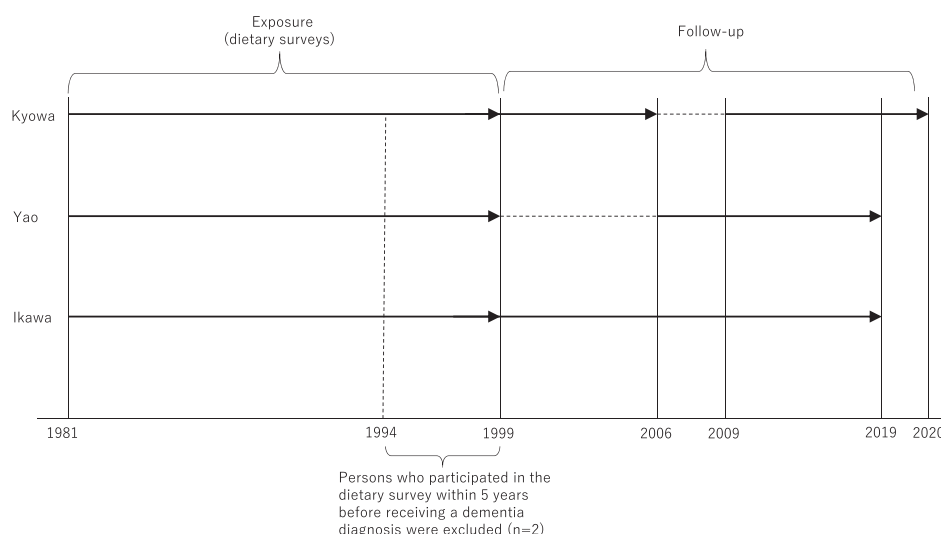


Figure 1. Dietary surveys were conducted from 1985 to 1999. They were followed up to confirm incident dementia from 1999 through 2020 (except for from April 2005 to April 2008, for which period the data were unavailable) in Kyowa; from 1999 through 2019 in Ikawa; and from 2006 through 2019 in Yao. Persons who participated in the dietary survey within 5 years before receiving a dementia diagnosis were excluded.

and insoluble fibers) as well as intake of each food group were calculated by using the Standard Tables of Food Composition in Japan (Seventh Revised Version).

Standard multivariate methods were applied for energy adjustment. Reproducibility of the 24-hour recall data was tested by comparison of the fiber intakes of the two studies conducted one year apart in 126 subsamples; the Spearman correlation coefficient was 0.28 for total fiber intake, 0.29 for soluble fiber intake, and 0.32 for insoluble fiber intake.

To determine whether associations would be observed in fiber-containing foods, we also examined the associations of potatoes, vegetables, and fruits (by which the partial R^2 for the proportion of the variance in total fiber intake explained was ≥ 0.05) with risk of disabling dementia. Grains and beans, although they yielded a high R^2 , were not tested here because the findings for these are supposed to be published elsewhere.

Other risk factors

Potential risk factors for disabling dementia were measured at the time of the dietary surveys. Well-trained study physicians or nurses measured the arterial systolic and fifth-phase diastolic blood pressures by using standard mercury sphygmomanometers on the right arm of the participants, who were quietly seated after having rested for at least 5 minutes. If the first systolic blood pressure reading was ≥ 140 mmHg and/or the diastolic blood pressure was ≥ 90 mmHg, the physicians or nurses repeated the measurement. For these

cases, the second reading was used in the analysis; otherwise, the first reading was used. Height without shoes and weight in light clothing were measured, and body mass index was calculated as weight in kilograms divided by height in meters squared. Face-to-face interviews were conducted to determine drinking (never, ex, or current) and smoking (never, ex, or current) statuses, amount of alcohol, number of cigarettes, antihypertensive medication, cholesterol-lowering medication, medication for diabetes, and a history of stroke. Serum glucose and total cholesterol were measured without a fasting requirement. Diabetes mellitus was defined as fasting serum glucose ≥ 126 mg/dL or non-fasting serum glucose ≥ 200 mg/dL, or being under medication for diabetes.

Statistical analysis

The age-adjusted means and proportions of the characteristics of the study participants at the dietary surveys were compared according to the quartiles of total fiber intake yielded by analyses of covariance. We conducted proportional hazards regression analyses to calculate the hazards ratios and 95% confidence intervals across the quartiles of total, soluble, and insoluble fiber intake and fiber-containing foods (potatoes, vegetables, and fruits) nested by the study communities and adjusted for age, sex, smoking status (never, ex, or current smokers of ≤ 20 or > 20 cigarettes/day), alcohol drinking (never, ex, or current drinkers of < 46 or ≥ 46 g ethanol/day), total energy intake (continuous), and fish, meat, and sodium consumptions (continuous), as

Table 1. Characteristics of participants according to quartiles of total fiber intake at dietary surveys, CIRCS, aged 40–64 years, 1981–99.

	Total fiber intake (g/day)				P for heterogeneity
	Q1 2.2–10.6	Q2 10.7–13.7	Q3 13.8–17.9	Q4 18.0–65.3	
Number	934	935	935	935	
Median fiber intake, g	8.9	12.3	15.6	21.4	
Age ^a , year	51.0	51.1	51.3	51.5	.38
Men ^b , %	50.5	43.8	41.4	40.9	<.001
Body mass index, kg/m ²	23.6	24.0	23.7	23.7	.05
Current smoker, %	29.0	27.2	26.7	26.7	.53
Current drinker, %	39.8	40.1	39.8	37.6	.38
Systolic blood pressure, mmHg	132	131	131	129	.006
Diastolic blood pressure, mmHg	82	81	82	80	.03
Antihypertensive medication, %	13.6	13.4	12.6	10.0	.06
Diabetes mellitus, %	4.8	5.2	5.3	3.8	.47
Serum total cholesterol, mg/Dl	201	199	201	199	.29
Cholesterol-lowering medication, %	1.8	2.6	2.2	2.0	.72
History of stroke, %	1.1	1.0	0.8	1.3	.71
Nutrient intake					
Total energy, kcal/day	1647	1852	2038	2368	<.001
Carbohydrate ^c , %kcal	64.1	63.7	64.0	63.8	.74
Fat, %kcal	21.3	21.8	21.5	21.8	.43
Protein, %kcal	14.6	14.6	14.5	14.4	.34
Grains, g/day	436	489	524	563	<.001
Potatoes, g/day	25.3	38.0	53.7	89.6	<.001
Beans, g/day	41.4	52.9	60.1	88.1	<.001
Vegetables, g/day	163	236	295	409	<.001
Fruits, g/day	73	119	155	232	<.001
Seaweeds, g/day	6.8	9.6	11.0	15.5	<.001
Mushrooms, g/day	3.3	5.5	7.9	10.3	<.001
Fishes, g/day	93	92	100	101	.01
Meats, g/day	43	48	49	56	<.001
Sodium, mg/day	3654	4149	4712	5822	<.001

^aSex-adjusted.^bAge-adjusted.^cCarbohydrates included alcohol.

Age and sex-adjusted unless specified otherwise.

potential confounders. For missing values for these variables (<5% of each variable), we set dummy variables and included them in the models. The linear trend for the hazard ratios across the categories was tested using the median value of each independent variable. Because we did not observe significant interactions among sex and any exposures in relation to risk of disabling dementia ($P > .05$), sex-specific analyses were not performed. All probability values for the statistical tests were two-tailed, and probability values below 0.05 were considered significant. All statistical tests were performed using SAS 9.4 software (SAS Institute, Cary, NC, U.S.A.).

Ethical consideration

Informed consent was obtained from community representatives. Individual consent was not required for the analysis of this study because it was conducted as a secondary use of data obtained for public health practice on cardiovascular disease prevention in the local community at that time. In accordance with relevant guidelines and regulations afterwards, the participants were retrospectively given the opportunity to withdraw their data

from analysis. The study was approved by the institutional review boards of the relevant institutions (Osaka Center of Cancer and Cardiovascular Disease Prevention, University of Tsukuba, and Osaka University).

Results

As shown in Table 1, men consumed less total fiber than did women. Systolic and diastolic blood pressures were inversely associated with total fiber intake. All food items, including fiber-containing foods (potatoes, vegetables, and fruits), and sodium were positively associated with total fiber intake.

During the follow-up (median, 19.7 years; maximum, 21.3 years), we observed a total of 670 cases of disabling dementia. Total fiber intake was inversely and linearly associated with risk of incident dementia (Table 2). The multivariate hazard ratios (95% confidence intervals) were 0.83 (0.67–1.04), 0.81 (0.65–1.02), and 0.74 (0.57–0.96) for individuals with the second, third, and highest quartiles of total fiber intake, respectively, compared with those with the lowest quartile (P for trend = .03). Of note, the association was not altered after

Table 2. Age- and sex-adjusted and multivariate hazard ratios and 95% confidence intervals of incident dementia according to quartiles of fiber intake.

	Men and Women				Trend <i>P</i>
	Total fiber intake (g/day)				
	Q1 2.2–10.6	Q2 10.7–13.7	Q3 13.8–17.9	Q4 18.0–65.3	
Person-years	14,478	14,658	15,252	15,294	
Total dementia					
Number of cases	170	160	163	177	
Model 1	1.0	0.81 (0.65–1.00)	0.79 (0.64–0.99)	0.74 (0.58–0.95)	.03
Model 2	1.0	0.83 (0.67–1.04)	0.81 (0.65–1.02)	0.74 (0.57–0.96)	.03
Dementia with a history of stroke					
Number of cases	32	24	27	30	
Model 1	1.0	0.70 (0.41–1.20)	0.82 (0.48–1.40)	0.82 (0.46–1.46)	.67
Model 2	1.0	0.72 (0.42–1.23)	0.83 (0.48–1.44)	0.89 (0.48–1.66)	.88
Dementia without a history of stroke					
Number of cases	116	107	97	97	
Model 1	1.0	0.77 (0.59–1.01)	0.68 (0.51–0.90)	0.62 (0.45–0.85)	.003
Model 2	1.0	0.81 (0.62–1.05)	0.68 (0.51–0.91)	0.59 (0.42–0.82)	.002

Model 1: Adjusted for age, sex, and total energy intake, and nested by area.

Model 2: Further adjusted for smoking status; alcohol drinking; and fish, meat, and sodium consumption.

Table 3. Age- and sex-adjusted and multivariate hazard ratios and 95% confidence intervals of incident dementia according to quartiles of intakes of soluble and insoluble fibers, and fiber-containing food groups.

	Total dementia				Trend <i>P</i>
	Q1	Q2	Q3	Q4	
Soluble fiber					
Median, g	1.7	2.5	3.3	4.6	
Person-years	14141	15116	14989	15436	
Number of cases	182	152	181	155	
Model 1	1.0	0.72 (0.58–0.89)	0.78 (0.63–0.96)	0.62 (0.49–0.79)	<.001
Model 2	1.0	0.72 (0.58–0.90)	0.77 (0.62–0.96)	0.61 (0.48–0.79)	<.001
Insoluble fiber					
Median, g	6.5	9.1	11.6	15.9	
Person-years	14572	14728	15205	15176	
Number of cases	167	151	173	179	
Model 1	1.0	0.80 (0.64–1.00)	0.87 (0.70–1.09)	0.78 (0.62–1.00)	.11
Model 2	1.0	0.82 (0.66–1.03)	0.89 (0.71–1.12)	0.79 (0.61–1.02)	.13
Potatoes					
Median, g	0	10	50	125	
Person-years	21288	7917	14973	15504	
Number of cases	279	83	144	164	
Model 1	1.0	0.81 (0.63–1.03)	0.65 (0.53–0.80)	0.80 (0.65–0.97)	.04
Model 2	1.0	0.81 (0.63–1.04)	0.65 (0.53–0.80)	0.79 (0.65–0.97)	.03
Vegetables					
Median, g	120	210	297	448	
Person-years	14704	15213	14574	15190	
Number of cases	151	166	163	190	
Model 1	1.0	1.08 (0.86–1.35)	0.96 (0.76–1.20)	1.05 (0.84–1.31)	.90
Model 2	1.0	1.08 (0.86–1.35)	0.98 (0.78–1.23)	1.06 (0.84–1.34)	.77
Fruits					
Median, g	0	45	150	328	
Person-years	16556	11957	15365	15804	
Number of cases	186	113	183	188	
Model 1	1.0	0.84 (0.66–1.06)	0.85 (0.69–1.04)	0.91 (0.74–1.14)	.71
Model 2	1.0	0.87 (0.68–1.10)	0.89 (0.72–1.10)	0.98 (0.78–1.22)	.87

Model 1: Adjusted for age, sex, and total energy intake, and nested by area.

Model 2: Further adjusted for smoking status; alcohol drinking; and fish, meat, and sodium consumption.

further adjustment for potential mediators (body mass index, systolic blood pressure, antihypertensive medication use, serum total cholesterol, cholesterol-lowering medication, and diabetes): the respective hazard ratios were 0.81 (0.65–1.02), 0.80 (0.64–1.01), and 0.75 (0.58–0.98) (*P* for trend = .05) (not shown in Table 2). The association of total fiber intake with disabling

dementia was confined to dementia without a history of stroke.

The inverse association with incident disabling dementia was more evident for soluble fiber intake and for potatoes, but not for vegetables or fruits (Table 3). The inverse association of soluble fiber was confined to dementia without a history of stroke

(Supplementary Table 1). The inverse association of potatoes was observed similarly for dementia with or without a history of stroke, but neither reached statistical significance.

Since the dementia registry data were unavailable between 2005 and 2008 in one community we studied, we conducted a sensitivity analysis starting follow-up from 2009. The associations did not change essentially: the multivariate hazard ratios (95% confidence intervals) of disabling dementia were 0.92 (0.72–1.17), 0.87 (0.68–1.12), and 0.75 (0.57–1.00) for individuals with the second, third, and highest quartiles of total fiber intake, respectively, as compared with those with the lowest quartile (P for trend = .04). The respective hazard ratios of disabling dementia without a history of stroke were 0.89 (0.66–1.19), 0.75 (0.55–1.03), and 0.59 (0.41–0.85) (P for trend = .003) (not shown in tables).

Discussion

We found an inverse association between dietary fiber intake, especially soluble fiber intake, and risk of disabling dementia in the Japanese population. The association was confined to disabling dementia cases without a history of stroke. This is the first prospective study to find an inverse association between dietary fiber intake and risk of dementia in a general population.

The mechanism explaining how dietary fiber reduces the risk of dementia warrants discussion. Fibers were reported to have beneficial effects on body weight, systolic blood pressure, serum lipids, and fasting glucose, and risks of stroke and diabetes [14], which could partly explain the association between fibers and dementia, especially vascular-type dementia. Another mechanism is that dietary soluble fiber regulates the composition of intestinal bacteria [1], and this composition was associated with the prevalence of dementia [3]. Animal studies have shown that dietary soluble fiber improved neuroinflammation [7] that is responsible for Alzheimer disease pathology [15] and that the gut-brain axis may have a role in the cerebral accumulation of amyloid protein such as amyloid- β [16], which is in line with the result of our study. However, another cross-sectional study found no significant correlation between fiber intake and plasma or brain amyloid- β [17]. We also need to note that having a high-fiber diet may reflect a diversity of dietary intake and that socioeconomic status may influence the risk of dementia. A systematic review reported a lower risk of dementia in persons with healthy dietary patterns

and Mediterranean diets, i.e. containing high dietary fiber [18], which is partially in line with our result.

We used the data of the compulsory national insurance to register dementia cases, which was a strength of this study. In this system, all individuals with disabling dementia who had applied for long-term care insurance in the communities were identified. The criteria for ‘the level of care required’ are uniformly determined throughout the country, and thus objectivity is guaranteed. On the other hand, using the data based on this system has several inevitable limitations, as previously discussed [19]. The diagnosis of ‘the grade of activities of daily living related to dementia’ was made by attending physicians, not psychiatrists. However, we previously did validate the diagnosis [12], as stated in the Methods. Further, we did not discriminate dementia into Alzheimer and vascular types. Instead, we used information on dementia with or without a history of stroke, assuming that dementia with a history of stroke is likely vascular-type dementia and that dementia without a history of stroke is likely Alzheimer-type dementia.

The other limitations of this study should be noted. First, the dietary surveys asked about meals taken in the last 24 hours. Thus, this survey method was inevitably affected by the foods that the participants happened to have eaten on the previous day or the day of the survey. Nevertheless, the probability of coincidentally eating something that the participant did not usually eat on the specific day of the survey should be small: the 1-year reproducibility of the survey methods was moderate ($r \approx 0.3$). Second, the dietary habits must have changed during the long follow-up. Especially in this study, the median time between the dietary survey (1985–99) and the start of follow-up (1999 or 2006) was 9 years. It should be noted that this study focused on the association between dietary fiber intake when the participants were aged 40–64 years before the start of follow-up and probably before the development of most dementia cases. Third, we did not have information on socioeconomic factors, which might be potential residual confounding factors [20]. The national surveys of Japanese representative samples showed a small positive association between household expenditure and total fiber intake (7.2 vs. 6.9 g/1000 kcal in men and 8.8 vs. 8.3 g/1000 kcal in women for the highest vs. lowest quartiles of household expenditure in 2003–7) [21], but no association between household income and potato intake, a main contributor of fiber intake in this study [22]. Last, we did not survey dementia at baseline, although we excluded participants who developed dementia within 5 years of the dietary survey, and the

median time from the dietary survey to dementia onset for cases was long (24 years). In addition, data on the dementia registry were unavailable in 1 community between 2005 and 2008. However, the sensitivity analyses following up all the participants from 2009 did not change the results materially. Therefore, the possibility of reverse causation and the impact of unavailable data should be small.

Conclusions

Dietary intake of fiber, especially soluble fiber, was inversely associated with risk of disabling dementia in a general Japanese population. This study should provide new insights into dietary factors that prevent dementia, which needs to be confirmed by further observational and/or intervention studies.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request and with the permission of the CIRCS committee.

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