



# Associations between dietary diversity and high sensitive C-reactive protein among Japanese workers: findings of a cross-sectional and longitudinal study

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## Abstract

**Purpose** To clarify the association between dietary diversity and inflammatory status in Japanese workers.

**Methods** Of 1,460 men and women aged 20–64 years in 2010 (baseline), those who were followed-up at least once between 2011 and 2018 were included in this study; 1,433 participants and 745 participants were included in the cross-sectional and longitudinal analyses, respectively. Dietary intake was assessed using a food frequency questionnaire at baseline, and the dietary diversity score was determined using the Quantitative Index for Dietary Diversity (QUANTIDD). High-sensitivity C-reactive protein (hs-CRP) was taken to indicate inflammatory status at the baseline and follow-up surveys. In the cross-sectional analysis using baseline data, a generalized linear model was used to calculate adjusted means and 95% confidence intervals (CIs) for hs-CRP according to the QUANTIDD score. In the longitudinal analysis, generalized estimating equations were used to calculate the adjusted mean (95% CI) for hs-CRP in follow-up according to the QUANTIDD score at baseline.

**Results** In the cross-sectional analysis, the hs-CRP concentration in male participants was significantly lower in those who had a high QUANTIDD score (adjusted mean [95% CI]: 0.074 [0.009–0.140] mg/dL in the lower group vs. 0.038 [-0.029–0.105] mg/dL in the higher group,  $p$ -value=0.034). In the longitudinal analysis, the hs-CRP concentration of male participants also tended to be lower in those with higher QUANTIDD scores ( $p$ -value=0.103). In both the cross-sectional and longitudinal analyses in women, there was no significant difference between the lower and higher QUANTIDD score groups.

**Conclusion** These findings suggest that, in male Japanese workers, higher dietary diversity might be important for maintaining a low inflammatory status.

**Keywords** Dietary diversity · Inflammatory · High sensitive C-reactive protein · Japanese worker · Cross-sectional study · Longitudinal study

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## Introduction

An unbalanced diet, characterized as containing an insufficient intake of healthy food, has become a public health problem in Japan. According to the National Health and Nutrition Survey, the intake of vegetables, fruits, and beans has been decreasing, and their intake is lowest in the 20–30-year age group in the Japanese population [1]. The Japanese dietary guidelines recommend eating a variety of food groups [2]. Previous studies conducted in countries other than Japan found that adherence to dietary diversity was associated with a low risk of non-communicable diseases [3–5].

High-sensitivity C-reactive protein (hs-CRP) is a known marker of inflammation that is associated with increased risk of chronic diseases such as type 2 diabetes mellitus [6, 7], cardiovascular disease [8–10], and many types of cancer [11–14].

Among the potential risk factors for chronic diseases, which include genetic and lifestyle factors, diet is one of the most modifiable [15]. Dietary factors modulate inflammatory status by suppressing immune responses [16]. Some previous studies have found that intake of some food groups, including cereals [17], fish and/or fish oil [16], and nuts [18], has the effect of significantly reducing inflammatory marker levels. In addition, several previous studies have demonstrated an association between dietary pattern type and inflammatory markers such as hs-CRP [19–25].

Many countries have developed nutritional policies for preventing chronic disease [26]. One such policy is dietary diversity, which has been shown to be critical in a high-quality diet [2, 27]. Dietary diversity varies among countries due to differences in dietary composition, food culture, and habitual dietary intake, and may influence the development of chronic diseases. However, the associations between dietary diversity and inflammatory markers such as hs-CRP in the Japanese population have yet to be elucidated. Thus, we analyzed both the cross-sectional and longitudinal associations between dietary diversity and hs-CRP concentration in Japanese workers.

## Methods and materials

### Study design and participants

The present cross-sectional analysis was based on data from the third wave (from June 2010 to February 2011) of an occupation-based dynamic cohort established in Tokushima Prefecture in Japan, the details of which have been reported elsewhere [28]. In brief, the participants underwent a voluntary health examination on an annual basis. The first

wave of the annual examination was conducted from June 2008 to February 2009 and involved 821 participants (550 men, 271 women; age range 20–60 years). The participants were followed up every year. New male and female workers aged  $\geq 20$  years were also recruited annually. After the fifth wave, participants' dietary intakes and physical activity were followed up by assessments performed every 5 years.

The present study participants were 1,460 men and women aged 20–64 years living in Tokushima Prefecture, Japan, in the third wave. Among these, those who had no or incomplete data for any inflammatory marker ( $n=5$ ), incomplete data for smoking habit, drinking habit, or physical activity, or a medical history of allergic diseases at baseline ( $n=13$ ) were excluded. Also excluded were participants who had a medical history of cancer, heart disease, or stroke at baseline ( $n=9$ ). The data of a final total of 1,433 participants (1,058 men and 375 women; age range, 20–64 years) were included in the cross-sectional analysis.

For the longitudinal analysis, we selected subjects who participated in the third-wave survey (baseline) and the fourth- to eleventh-wave surveys (follow-up surveys) at least once: the fourth study survey (June 2011 to February 2012,  $n=1,349$ ), fifth study survey (June 2012 to February 2013,  $n=1,399$ ), sixth study survey (June 2013 to February 2014,  $n=1,432$ ), seventh study survey (June 2014 to February 2015,  $n=1,414$ ), eighth study survey (June 2015 to February 2016,  $n=1,431$ ), ninth study survey (June 2016 to February 2017,  $n=1,455$ ), tenth study survey (June 2017 to February 2018,  $n=1,394$ ), and eleventh study survey (June 2018 to February 2019,  $n=1,373$ ). Although we also conducted surveys after 2019, we thought that the COVID-19 pandemic would affect the assessment of hs-CRP, so a longitudinal analysis using data from the third- to eleventh-wave surveys was conducted. Of the 1,433 participants included in the cross-sectional analysis, those who did not participate in the follow-up survey at least once were excluded ( $n=230$ ). Almost all of the reasons for missing data in the present study were random events, such as moving out of the prefecture, changing jobs to another company, retiring, or cancelling the measurement visit due to work schedule changes. A final total of 1,203 subjects (886 men and 317 women) were included in the longitudinal analysis (Fig. 1).

The study was conducted according to the ethical standards of the Declaration of Helsinki, and the protocol was approved by the institutional review board of Tokushima University Hospital (ethical approval No. 2868). Written, informed consent was obtained from all participants.

### Dietary assessment

The participants were asked about meals taken in the past one month and used a food frequency questionnaire (FFQ)

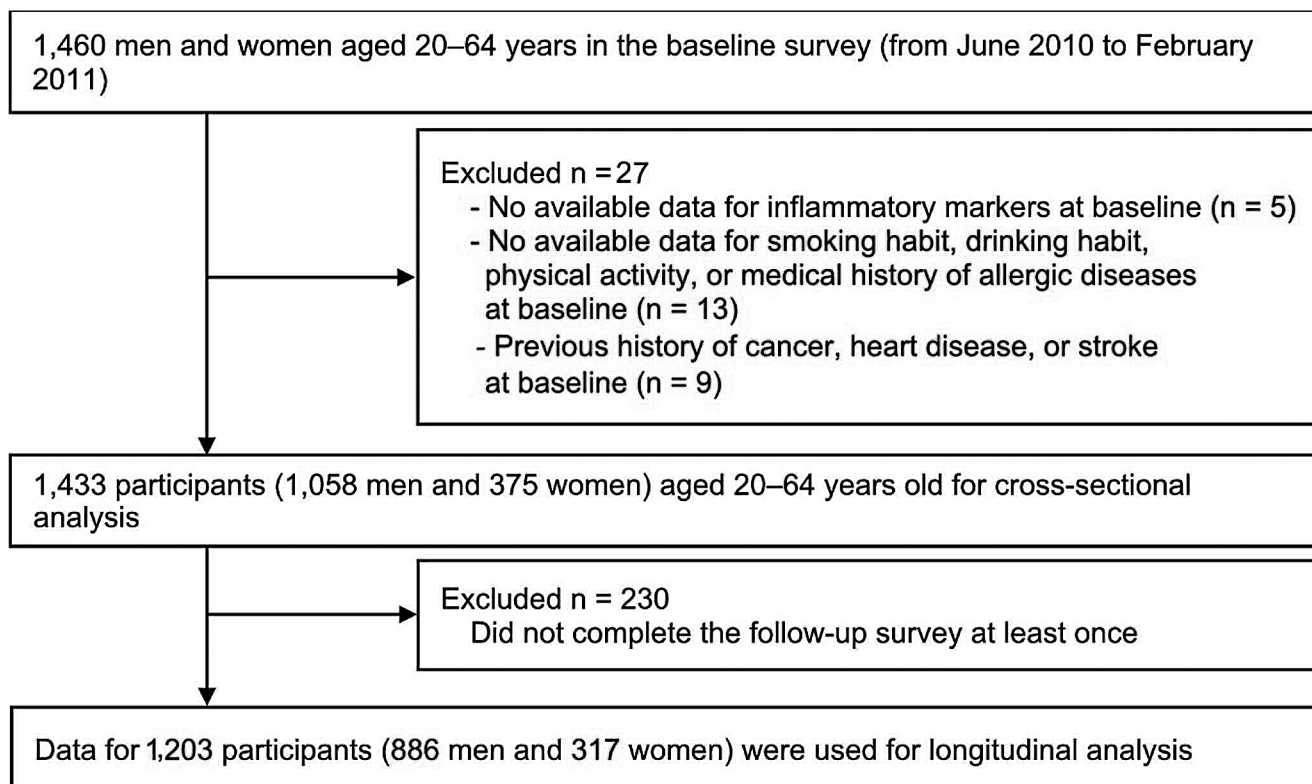


Fig. 1 Flow chart of participant selection

to determine the frequency of food intake (FFQg ver. 2.0; Kenpakusha Inc., Tokyo, Japan). Participants were asked about the frequency and amount of all foods consumed at each meal, and they were asked how many times and how much of each of the food groups was consumed per week. The amount of food consumed (per week) was calculated as the product of frequency of eating and the amount of each food at each meal; in the FFQg, such food intake is calculated for the following 17 food groups: cereals; potatoes and starches; deep yellow vegetables; other vegetables and mushrooms; algae; pulses; fish, mollusks and crustaceans; meat; eggs; milk and milk products; fruits; confectionaries; beverages; sugar and sweeteners; nuts and seeds; fats and oils; seasonings and spices [29]. The validity of the FFQg was verified by comparing food intake amounts for seven consecutive days using the weighting method [30].

The dietary diversity score was calculated using the Quantitative Index for Dietary Diversity (QUANTIDD) developed by Katanoda et al. [31]. The QUANTIDD score is calculated as the proportion of foods that contribute to total energy, for the amount of food and the number of food groups, following the formula:

$$\text{QUANTIDD} = \frac{1 - \sum_j^n \text{prop}(j)^2}{1 - \frac{1}{n}}$$

, where  $\text{prop}(j)$  is the proportion of each food group(s)  $j$  contributing to total energy or nutrient intake, and  $n$  is the number of food groups. The possible score ranges from 0 to 1. In the present study, we estimated scores based on the intake of 12 main food groups, excluding confectionaries, beverages, sugar and sweeteners, fats and oils, and seasonings and spices. Beverages were excluded as components of dietary diversity in this study. Beverages are liquid foods that have a different density than solid foods. In addition, beverages in the Japanese food composition table include many kinds of liquid foods that might affect chronic outcomes differently, such as alcohol, tea, coffee, and soft drinks (fruit-flavored and colored drinks), but not including fresh fruit juice or milk. The reason for the exclusion of beverages as a component of the dietary diversity score was to avoid difficulties in measuring beverages that contain a mix of alcohol, tea, and soft drinks. In addition, confectionaries, sugar and sweeteners, fats and oils, and seasonings and spices were also excluded in this study. The dietary guidelines do not recommend the consumption of sugary food (including added sugar), sodium, and saturated fat. These food groups, such as confectionaries, sugar and sweeteners, fats and oils, and seasonings and spices, include non-recommended nutrient contents (added sugar, sodium, and saturated fat). The reason for the exclusion of confectionaries, sugar and sweeteners, fats and oils, and seasonings and spices was to avoid

difficulty in interpreting dietary diversity including non-recommended food groups. In addition, because the range of QUANTIDD scores is narrow, we divided the participants into two groups by QUANTIDD score using a sex-specific median (higher group: above median value, lower group: below median) to more clearly assess the effect of QUANTIDD score differences. In this study, the lower group was defined as the control group.

Dietary patterns as a correlation matrix for the 17 food groups were assessed using principal component factor analysis. The principal components were selected on the basis of eigenvalues  $> 1.3$  and interpretability (Supplemental Table 1). Principal component scores were saved for each individual and were used as continuous variables. The first principal component was termed the “healthy pattern” and contained higher factor loadings for the ten food groups: cereals; potatoes and starches; deep yellow vegetables; other vegetables and mushrooms; algae; pulses; fish, mollusks and crustaceans; fruits; sugars and sweeteners; and seasonings and spices. This pattern explained 21.6% of the variance. The second principal component, termed the “Western pattern”, contained higher factor loadings for the four food groups of meat, eggs, beverages, and fats and oils, and it explained 9.5% of the variance. The third component, termed the “sweetener pattern”, contained higher factor loadings for the three food groups of milk and milk products, confectionaries, and nuts and seeds, and it explained 7.7% of the variance. The scores of the three principal components were saved for each participant and used in the analysis.

### Blood inflammatory markers

For serum biochemical measurements in both the baseline survey and all follow-up surveys, venous blood was taken via an antecubital vein in the morning of the survey, and all hs-CRP values were measured. The participants were requested not to eat from after dinner to the time of examination the next day as much as possible and underwent the medical health check-up the following day at their worksite. Hs-CRP concentration was determined using a commercially available latex turbidimetric immunoassay (LT CRP-HS II, Wako Pure Chemical Ltd., Osaka, Japan).

### Other measurements

The following measurements were also collected at baseline in this study. Height was measured to the nearest 0.1 cm, with participants standing without shoes or sandals. Body weight was measured to the nearest 100 g, with participants wearing light clothing. The body mass index (BMI) was calculated using the formula:  $BMI = \text{weight (kg)} / [\text{height (m)}]^2$ .

Daily values of physical activity (MET-hours/week) were calculated using the International Physical Activity Questionnaire [32]. The following information was obtained by a self-administered questionnaire: medical history of hypertension and allergy (binary: yes or no), education level (categorical: elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other), drinking habit (categorical: current, former, never), and smoking habit (categorical: current, former, never). Subjects completed the questionnaire before attending the physical examination day.

### Statistical analysis

The basic characteristics of participants by the QUANTIDD score were dichotomized by sex. Continuous variables are presented as mean  $\pm$  standard deviation (SD) or median (25 percentile, 75 percentile) values, and simple mean comparisons were calculated using Student's *t*-test or the Mann–Whitney test. Categorical variables are expressed as numbers (percentages, %), and proportions were compared using the chi-squared test.

The confounding variables defined in this study included baseline age, energy intake [33], BMI [34], physical activity [35], smoking habit [36], drinking habit [37], education level [38], medical history of hypertension [8–10, 39], allergy [40], and dietary patterns in both cross-sectional and longitudinal analyses.

In the cross-sectional analysis, a generalized linear model was used to calculate the adjusted mean and 95% confidence interval (CI) for hs-CRP by the QUANTIDD score after controlling for the following variables; when the hs-CRP level was compared between two groups (lower group and higher group) of the QUANTIDD score, the lower group of the QUANTIDD score was used as the reference group. The confounding variables were (1) age-adjusted model, age (continuous: years); (2) Model 1, age-adjusted model + energy intake (continuous: kcal/day), BMI (continuous:  $\text{kg}/\text{m}^2$ ), physical activity (continuous: MET-hours/week), smoking habit (categorical: current, former, never), drinking habit (categorical: current, former, never), education level (categorical: elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other), and medical history of hypertension and allergy (binary: yes, no); (3) Model 2, Model 1 + healthy dietary pattern (continuous: score); (4) Model 3, Model 1 + Western dietary pattern (continuous: score); and (5) Model 4, Model 1 + sweetener dietary pattern (continuous: score).

In the longitudinal analysis, cumulative data during follow-up surveys were analyzed using generalized estimating equations (GEEs). GEEs take into account the dependency

of repeated observations within participants. An additional advantage of GEEs is that missing values can also be used during the analysis. Thus, subjects who were lost to follow-up surveys after the baseline survey were also included in the analyses. GEE models were fitted by the GENLIN syntax in SPSS. This procedure corresponds to generalized linear models. In the present analyses, compound symmetry was specified for the correlation structure. GEE analyses were used to estimate the adjusted mean and 95% CI for hs-CRP in the follow-up surveys by the QUANTIDD score at baseline after controlling for the following variables; when the cumulative hs-CRP level was compared between two groups (lower group and higher group) of the QUANTIDD score, the lower group of the QUANTIDD score was used as the reference group. The confounding variables were: (1) age-adjusted model, age and follow-up time (continuous: years); (2) Model 1, Age-adjusted model+energy intake, BMI, physical activity, smoking habit, drinking habit, education level, and medical history of hypertension and allergy; (3) Model 2, Model 1+healthy dietary pattern; (4) Model 3, Model 1+Western dietary pattern; and (5) Model 4, Model 1+sweetener dietary pattern.

As one of the sensitivity analyses (total number=1,203, cumulative number=8,003), the longitudinal association between the QUANTIDD score and hs-CRP was assessed using both baseline (2010) and follow-up dietary data (2011, 2012 and 2017). In addition, as another sensitivity analysis (total number=1,203, cumulative number=10,827), the longitudinal association between the QUANTIDD score and hs-CRP after imputing missing outcome data with estimated mean values from previously measured outcome data, when information about hs-CRP level during follow-up was lost, was confirmed.

All statistical analyses were performed separately for each sex using SPSS (IBM Corporation, Tokyo, Japan) version 28.0 for Windows. All statistical tests were based on two-sided probabilities. All *p*-values < 0.05 were considered significant.

## Results

### Participants' characteristics

Table 1 lists the participants' characteristics by QUANTIDD score and sex in the cross-sectional analysis. In men and women, the higher QUANTIDD score groups tended to have higher dietary diversity scores (*p*-value < 0.001). In both sexes, there was also a greater number of participants with a current drinking habit in the higher QUANTIDD score group than in the lower group. In women, participants who had higher dietary diversity tended to be older, and

there was a greater number of participants with higher education in men according to QUANTIDD score.

Table 2 lists the cumulative number of participants and follow-up ratio in the longitudinal analysis. The cumulative number of participants was 5,990 for men and 2,013 for women. During the 8-year follow-up period, the mean cumulative follow-up years were  $4.08 \pm 2.29$  years for men and  $4.01 \pm 2.33$  years for women, and mean cumulative participation was  $6.78 \pm 2.46$  times for men and  $6.35 \pm 2.56$  times for women.

Table 3 shows the participant characteristics by QUANTIDD score and sex in the longitudinal analysis. The participants' basic characteristics were similar in both the longitudinal and cross-sectional analyses.

### Association of the dietary diversity score with hs-CRP

In the cross-sectional analysis (Table 4), the age-adjusted mean and 95% CI of hs-CRP in male participants were lower in the higher QUANTIDD score group (0.084 [0.061–0.107] mg/dL) than in the lower QUANTIDD score group (0.116 [0.093–0.139] mg/dL) (*p*-value=0.057). Table 4 shows the multivariate-adjusted mean and 95% CI of hs-CRP according to the QUANTIDD score in the cross-sectional analysis (Model 1). In male participants, the adjusted mean and 95% CI of hs-CRP were significantly lower in the higher QUANTIDD score group (0.038 [-0.029–0.105] mg/dL) than in the lower QUANTIDD score group (0.074 [0.009–0.140] mg/dL) (*p*-value=0.034). To determine whether the associations between dietary diversity and hs-CRP were confounded by dietary quality, such as dietary pattern, we further adjusted the scores for healthy dietary pattern, Western dietary pattern, and sweetener dietary pattern. After controlling for each dietary pattern score, a significant inverse association between the QUANTIDD score and hs-CRP was maintained in men. The adjusted mean and 95% CI for hs-CRP were 0.078 (0.011–0.145) mg/dL in the lower QUANTIDD score group and 0.035 (-0.033–0.102) mg/dL in the higher QUANTIDD score group (*p*-value=0.030) after controlling for healthy dietary pattern score. After controlling for Western dietary pattern score, the adjusted mean and 95% CI for hs-CRP were 0.074 (0.009–0.140) mg/dL in the lower QUANTIDD score group and 0.037 (-0.030–0.104) mg/dL in the higher QUANTIDD score group (*p*-value=0.028). After controlling for sweetener dietary pattern score, the adjusted mean and 95% CI for hs-CRP were 0.074 (0.009–0.140) mg/dL in the lower QUANTIDD score group and 0.038 (-0.028–0.105) mg/dL in the higher QUANTIDD score group (*p*-value=0.034).



**Table 1** Participants' characteristics according to dietary diversity score group and sex in the cross-sectional analysis<sup>§§</sup>

	Men		Women		<i>p</i> -value
	Lower group ( <i>n</i> =529)	Higher group ( <i>n</i> =187)	Lower group ( <i>n</i> =187)	Higher group ( <i>n</i> =188)	
Dietary diversity score <sup>§</sup>	0.734 (0.704, 0.795)	0.874 (0.847, 0.897)	0.795 (0.761, 0.842)	0.899 (0.880, 0.918)	<0.001
Age (y) †, ††	39.9 ±9.5	40.5 ±9.8	37.4 ±9.1	40.2 ±10.2	0.007
Body mass index (kg/m <sup>2</sup> ) †, ††	23.8 ±3.4	23.9 ±3.2	21.4 ±3.3	21.5 ±3.0	0.643
Physical activity (yes) †, †††	254 (48.0)	298 (56.3)	83 (44.4)	96 (51.1)	0.195
Education level †, ††					<0.001
Elementary, junior high school, and high school	117 (22.1)	80 (15.1)	40 (21.4)	34 (18.1)	
Tertiary college, career college, and junior college	107 (20.2)	67 (12.7)	34 (18.2)	31 (16.5)	
College and graduate school	175 (33.1)	234 (44.2)	54 (28.9)	69 (36.7)	
Other	2 (0.4)	8 (1.5)	9 (4.8)	5 (2.7)	
Unknown	128 (24.2)	140 (26.5)	50 (26.7)	49 (26.1)	
Smoking habit †, †††					0.340
Current	210 (39.7)	160 (30.2)	16 (8.6)	10 (5.3)	
Former	101 (19.1)	132 (25.0)	11 (5.9)	8 (4.3)	
Never	218 (41.2)	237 (44.8)	160 (85.6)	170 (90.4)	
Drinking habit †, †††					0.038
Current	281 (53.1)	329 (62.2)	55 (29.4)	77 (41.0)	
Former	20 (3.8)	10 (1.9)	2 (1.1)	4 (2.1)	
Never	228 (43.1)	190 (35.9)	130 (69.5)	107 (56.9)	
Medical history †, †††					
Allergy (+)	213 (40.3)	223 (42.2)	101 (54.0)	105 (55.9)	0.720
Hypertension (+)	19 (3.6)	15 (2.8)	4 (2.1)	2 (1.1)	0.407
High sensitivity C-reactive protein (mg/dL) <sup>§</sup>	0.04 (0.02, 0.09)	0.04 (0.02, 0.09)	0.196 (0.01, 0.04)	0.02 (0.01, 0.05)	0.614

† Mean ± standard deviation † Number (%) † Median (25th, 75th percentile).

†† Student's *t*-test or Welch's *t*-test was used to calculate the *p*-value.

††† Mann–Whitney U-test was used to calculate the *p*-value.

§§ The chi-squared test was used to calculate the *p*-value.

§§ QUANTILDD score: Lower group: 0–0.8223, Higher group: 0.8224–1.00 for men; Lower group: 0–0.8638, Higher group: 0.8639–1.00 for women

**Table 2** Participation during the follow-up period

Follow-up year	Men		Women	
	Number of participants	Follow-up ratio (%)	Number of participants	Follow-up ratio (%)
2010	886	-	317	-
2011	848	( 95.7 )	305	( 96.2 )
2012	791	( 89.3 )	277	( 87.4 )
2013	684	( 77.2 )	225	( 71.0 )
2014	626	( 70.7 )	200	( 63.1 )
2015	585	( 66.0 )	174	( 54.9 )
2016	561	( 63.3 )	176	( 55.5 )
2017	522	( 58.9 )	172	( 54.3 )
2018	487	( 55.0 )	167	( 52.7 )
Cumulative number	5,990		2,013	
Mean cumulative follow-up (y) ‡	4.08 ± 2.29		4.01 ± 2.33	
Mean cumulative participation (times) ‡	6.78 ± 2.46		6.35 ± 2.56	

‡ Mean ± standard deviation

**Table 3** Participants’ characteristics at baseline according to dietary diversity score group and sex in the longitudinal analysis<sup>§§</sup>

	Men		<i>p</i> -value	Women		<i>p</i> -value
	Lower group ( <i>n</i> =443)	Higher group ( <i>n</i> =443)		Lower group ( <i>n</i> =158)	Higher group ( <i>n</i> =159)	
Dietary diversity score <sup>§</sup>	0.764 ( 0.704, 0.795 )	0.872 ( 0.847, 0.898 )	<0.001	0.814 ( 0.771, 0.843 )	0.895 ( 0.878, 0.916 )	<0.001
Age (y) †, ¶	39.4 ± 9.3	40.3 ± 9.8	0.146	37.9 ± 9.3	40.2 ± 10.0	0.032
Body mass index (kg/m <sup>2</sup> ) †, ¶	23.6 ± 3.2	23.8 ± 3.2	0.374	21.4 ± 3.3	21.4 ± 2.7	0.957
Physical activity (yes) †, ‡‡	228 ( 51.5 )	192 ( 43.3 )	0.18	87 ( 55.1 )	80 ( 50.3 )	0.432
Education level †, ‡‡			<0.001			0.425
Elementary, junior high school, and high school	117 ( 26.4 )	80 ( 18.1 )		40 ( 25.3 )	34 ( 21.4 )	
Tertiary college, career college, and junior college	107 ( 24.2 )	67 ( 15.1 )		35 ( 22.2 )	30 ( 18.9 )	
College and graduate school	174 ( 39.3 )	235 ( 53.0 )		54 ( 34.2 )	69 ( 43.4 )	
Other	2 ( 0.5 )	8 ( 1.8 )		9 ( 5.7 )	5 ( 3.1 )	
Unknown	43 ( 9.7 )	53 ( 12.0 )		20 ( 12.7 )	21 ( 13.2 )	
Smoking habit †, ‡‡			0.033			0.425
Current	171 ( 38.6 )	139 ( 31.4 )		11 ( 7.0 )	7 ( 4.4 )	
Former	187 ( 42.2 )	193 ( 43.6 )		138 ( 87.3 )	146 ( 91.8 )	
Never	85 ( 19.2 )	111 ( 25.1 )		9 ( 5.7 )	6 ( 3.8 )	
Drinking habit †, ‡‡			<0.001			0.020
Current	230 ( 51.9 )	285 ( 64.3 )		42 ( 26.6 )	64 ( 40.3 )	
Former	197 ( 44.5 )	149 ( 33.6 )		114 ( 72.2 )	91 ( 57.2 )	
Never	16 ( 3.6 )	9 ( 2.0 )		2 ( 1.3 )	4 ( 2.5 )	
Medical history †, ‡‡						
Allergy (+)	260 ( 58.7 )	253 ( 57.1 )	0.683	71 ( 44.9 )	69 ( 43.4 )	0.821
Hypertension (+)	9 ( 2.0 )	6 ( 1.4 )	0.604	4 ( 2.5 )	1 ( 0.6 )	
High sensitivity C-reactive protein (mg/dL) <sup>§</sup>	0.04 ( 0.02, 0.08 )	0.04 ( 0.02, 0.09 )	0.118	0.02 ( 0.01, 0.05 )	0.02 ( 0.01, 0.05 )	0.219

† Mean ± standard deviation ‡ Number (%) § Median (25th, 75th percentile).

¶ Student’s *t*-test or Welch’s *t*-test was used to calculate the *p*-value.

†† Mann–Whitney U-test was used to calculate the *p*-value.

‡‡ The chi-squared test was used to calculate the *p*-value.

§§ QUANTIDD score: Lower group: 0–0.8228, Higher group: 0.8229–1.00 for men; Lower group: 0–0.8649, Higher group: 0.8650–1.00 for women

**Table 4** Adjusted mean of hs-CRP (mg/dL) according to dietary diversity score group and sex in the cross-sectional analysis<sup>†,‡,§,¶</sup>

	Lower group	Higher group	<i>p</i> -value
<i>Men (n=1,058)</i>			
Age-adjusted model <sup>§</sup>	0.116	(0.093 - 0.139)	0.057
Model 1 <sup>¶</sup>	0.074	(0.009 - 0.140)	0.034
Model 2 <sup>¶¶</sup>	0.078	(0.011 - 0.145)	0.030
Model 3 <sup>¶¶</sup>	0.074	(0.009 - 0.140)	0.028
Model 4 <sup>¶¶</sup>	0.074	(0.009 - 0.140)	0.034
<i>Women (n=375)</i>			
Age-adjusted model <sup>§</sup>	0.051	(0.034 - 0.069)	0.657
Model 1 <sup>¶</sup>	0.049	(-0.005 - 0.102)	0.459
Model 2 <sup>¶¶</sup>	0.051	(-0.002 - 0.105)	0.204
Model 3 <sup>¶¶</sup>	0.048	(-0.005 - 0.102)	0.510
Model 4 <sup>¶¶</sup>	0.048	(-0.005 - 0.101)	0.455

<sup>†</sup> Adjusted mean (95% confidence interval).

<sup>‡</sup> Generalized linear models were used to calculate the *p*-value.

<sup>§</sup> Age-adjusted model: age (continuous, years).

<sup>¶</sup> Model 1: Age adjusted model + energy intake (continuous, kcal/day), body mass index (continuous, kg/m<sup>2</sup>), physical activity (continuous, MET-hours/week), smoking habit (categorical; current, former, never), drinking habit (categorical; current, former, never), education (categorical; elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other), and medical history of hypertension and allergy (binary; yes, no).

<sup>¶¶</sup> Model 2: Model 1 + healthy dietary pattern (continuous, score).

<sup>¶¶</sup> Model 3: Model 1 + Western dietary pattern (continuous, score).

<sup>¶¶</sup> Model 4: Model 1 + sweetener dietary pattern (continuous, score).

<sup>¶¶¶</sup> QUANTITIDD score: Lower group: 0–0.8223, Higher group: 0.8224–1.00 for men; Lower group: 0–0.8638, Higher group: 0.8639–1.00 for women



Table 5 shows the multivariate-adjusted mean and 95% CI of hs-CRP according to QUANTIDD score in the longitudinal analysis. In this analysis, men in the higher QUANTIDD score group tended to have a lower concentration of hs-CRP (adjusted mean and 95% CI: 0.099 [0.076–0.122] mg/dL in the lower QUANTIDD score group vs. 0.084 [0.062–0.105] mg/dL in the higher QUANTIDD score group,  $p$ -value=0.103), though the difference was not significant (Model 1). In addition, after controlling for each dietary pattern score, a slight inverse association was maintained in men between QUANTIDD score and hs-CRP ( $p$ -value=0.136 in Model 2, 0.098 in Model 3, and 0.103 in Model 4).

In women, there was no significant association between dietary diversity and hs-CRP in either the cross-sectional or longitudinal analysis.

To assess the longitudinal association between the QUANTIDD score and hs-CRP levels using both baseline and follow-up dietary data, a sensitivity analysis (total number=1,203, cumulative number=8,003) was performed and showed similar associations using both baseline and follow-up dietary data (Supplemental Table 4). In addition, a sensitivity analysis was performed using an imputed dataset (total number=1,203, cumulative number=10,827), and it showed similar associations using the imputed dataset (Supplemental Table 5). Thus, the main associations between the QUANTIDD score and hs-CRP levels were robust.

## Discussion

The present study showed that, in the cross-sectional analysis, hs-CRP concentration in men was significantly lower in those who had a higher QUANTIDD score (Table 4). The longitudinal analysis also showed that hs-CRP concentration tended to be lower in men who had a higher QUANTIDD score, and was close to significance (Table 5). In women, however, no significant difference in hs-CRP concentration was observed between those with lower and higher QUANTIDD scores. In two sensitivity analyses, similar longitudinal associations were found in both sexes (Supplemental Tables 4 and 5).

An inverse association between dietary diversity and concentration of hs-CRP was shown in the present male Japanese workers (Tables 4 and 5, and Supplemental Tables 4 and 5). These results are consistent with those of several previous studies that investigated the association between dietary pattern and serum CRP concentration [20, 22, 23, 25]. Although some previous studies have reported that a Western dietary pattern (i.e., high intakes of red meat, refined grains, processed meat, and high-fat dairy products) is associated with increased concentration of serum

CRP [19–22], an association between the healthy and/or prudent dietary pattern (e.g., high intakes of vegetables, fruit, and fish) and decreased concentration of serum CRP has also been reported [20, 22, 23]. In particular, two cross-sectional studies conducted in the Japanese population [23, 25] showed that a healthy or prudent dietary pattern decreased the serum CRP concentration. The present participants consumed higher amounts of vegetables, fruit, soy, and fish and lower amounts of cereals as the QUANTIDD score increased (Supplemental Tables 2 and 3). Therefore, the dietary diversity score used in the present study might reflect the dietary characteristics of each of the healthy, prudent, and non-Western dietary patterns. We further adjusted the healthy dietary pattern score to determine whether the associations between dietary diversity and hs-CRP were confounded by dietary quality, and we found that a significant inverse association between the QUANTIDD score and hs-CRP was maintained in men (Table 4). Furthermore, after controlling for Western dietary pattern score, a significant inverse association was clear in men (Table 4). The present results and those of previous studies suggest that a higher dietary diversity score, which indicates healthier dietary characteristics, might reduce the concentration of hs-CRP in Japanese adults. Accordingly, eating a variety of food groups might have direct protective effects against inflammatory markers in addition to the effects mediated by diet quality.

The possible reason for the present results is that a higher dietary diversity score indicates healthier nutritional habits. It has been shown that dietary diversity is related to food quality [27]. Furthermore, diets with greater variety are associated with increased intakes of essential micronutrients including vitamin C, calcium, and dietary fiber, while having low carbohydrate intake [41]. Indeed, the present study participants who had high QUANTIDD scores consumed higher amounts of several healthy food groups: deep yellow vegetables; other vegetables and mushrooms; algae; pulses; fish, mollusks and crustaceans; milk and milk products; and fruits, nuts, and seeds. Previous studies have reported that the beneficial combinations of antioxidant vitamins and fiber contained in some food groups, including deep yellow vegetables, other vegetables and mushrooms, algae, pulses and fruit, may partly explain this inverse association between healthy dietary pattern and CRP [42–44]. Thus, consuming various types of foods that suggest higher dietary quality might be associated with decreased hs-CRP, through protective actions such as antioxidant activity by nutrients such as antioxidants.

In the present study, the association between dietary diversity and concentration of hs-CRP differed between men and women (Tables 4 and 5, and Supplemental Tables 4 and 5). This might mean that the effect of dietary diversity

**Table 5** Adjusted mean hs-CRP (mg/dL) according to dietary diversity score group and sex in longitudinal analysis<sup>†,‡,§,¶,¶¶</sup>

	Lower group	Higher group	<i>p</i> -value
<i>Men (baseline n=886, cumulative n=5,990)</i>			
Age-adjusted model <sup>§</sup>	0.115	(0.097 - 0.133)	(0.087 - 0.111)
Model 1 <sup>¶</sup>	0.099	(0.076 - 0.122)	(0.062 - 0.105)
Model 2 <sup>¶¶</sup>	0.099	(0.076 - 0.121)	(0.062 - 0.107)
Model 3 <sup>¶¶</sup>	0.100	(0.077 - 0.123)	(0.061 - 0.105)
Model 4 <sup>¶¶¶</sup>	0.099	(0.076 - 0.122)	(0.061 - 0.105)
<i>Women (baseline n=317, cumulative n=2,013)</i>			
Age-adjusted model <sup>§</sup>	0.058	(0.047 - 0.069)	(0.043 - 0.081)
Model 1 <sup>¶</sup>	0.058	(0.029 - 0.087)	(0.031 - 0.088)
Model 2 <sup>¶¶</sup>	0.057	(0.028 - 0.087)	(0.033 - 0.090)
Model 3 <sup>¶¶</sup>	0.055	(0.022 - 0.088)	(0.029 - 0.089)
Model 4 <sup>¶¶¶</sup>	0.060	(0.030 - 0.089)	(0.032 - 0.090)

<sup>†</sup> Cumulative adjusted mean (95% confidence interval).

<sup>‡</sup> Cumulative data during follow-up surveys were analyzed using generalized estimating equations. Generalized estimating equations were used to calculate the *p*-value.

<sup>§</sup> Age-adjusted model: age (continuous, years), survey year (continuous, years).

<sup>¶</sup> Model 1: Age adjusted model + energy intake (continuous, kcal/day), body mass index (continuous, kg/m<sup>2</sup>), physical activity (continuous, MET-hours/week), smoking habit (categorical; current, former, never), drinking habit (categorical; current, former, never), education (categorical; elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other) and medical history of hyper tension and allergy (binary; yes, no).

<sup>¶¶</sup> Model 2: Model 1 + healthy dietary pattern (continuous, score).

<sup>¶¶¶</sup> Model 3: Model 1 + western dietary pattern (continuous, score).

<sup>¶¶¶¶</sup> Model 4: Model 1 + sweetener dietary pattern (continuous, score).

<sup>¶¶¶¶¶</sup> QUANTITDD score: Lower group: 0–0.8228, Higher group: 0.8229–1.00 for men; Lower group: 0–0.8649, Higher group: 0.8650–1.00 for women

on inflammatory markers such as hs-CRP is stronger in men than in women. It is known that factors such as age [45], body mass [34], and sex hormones [46, 47] are related to inflammatory status. In the present study, female participants had healthier demographic factors (e.g. higher dietary diversity, younger age, higher proportion of normal body type) than those in men. These characteristics might reduce the variation of hs-CRP more in women than in men: the median concentration of hs-CRP (interquartile range) at baseline was 0.040 (0.020–0.083) mg/dL in men and 0.020 (0.010–0.050) mg/dL in women ( $p$ -value < 0.001) (data not shown). Therefore, a dietary diversity effect might have been seen in men with more variable hs-CRP. Another possible reason for the sex difference is a difference in variation of the QUANTIDD score. The present female participants had higher dietary diversity than did the male participants: the median QUANTIDD score (interquartile range) at baseline was 0.82 (0.76–0.87) mg/dL in men and 0.86 (0.81–0.90) mg/dL in women ( $p$ -value < 0.001) (data not shown).

The present study has some limitations. First, the present study included both cross-sectional and longitudinal analyses. Although the follow-up time was probably not too short (the median cumulative follow-up was 4 years) to assess changes in outcome, the follow-up rate decreased to about half in subsequent follow-up years (Table 2). To minimize this effect, we used GEE models in which missing values can also be used during analysis. Almost all previous studies that have assessed the association between dietary pattern and CRP level were cross-sectional in design [19–25]. Therefore, longitudinal study findings are important for this research area. In addition, there were no significant differences in blood pressure, blood glucose, or BMI between the two QUANTIDD score groups for about 8 years in the present population (data not shown), whereas in contrast, the trend for hs-CRP approached significance. Since high concentrations of hs-CRP, indicating a chronic inflammatory state, occur in the pre-stages of various lifestyle-related diseases (e.g. hypertension, diabetes mellitus, and obesity), inflammatory markers such as hs-CRP might be useful predictors of lifestyle-related disease. Second, since the study participants lived in a limited area and included only Japanese workers, the present findings might not be generalizable to other populations. We acknowledge that more detailed information regarding occupation type is important, but these data could not be obtained. Third, the sample size of this study, especially in women, was small. Fourth, food consumption was assessed only at baseline. When the secular change of the QUANTIDD score during the 8 follow-up years was confirmed, there were no significant change in women, but there was a U-shaped secular change in men during follow-up (Supplemental Table 6). Therefore, the longitudinal association between the QUANTIDD score

and hs-CRP was assessed using both baseline and follow-up dietary data as a sensitivity analysis, and a similar longitudinal association was confirmed (Supplemental Table 4). Thus, the main associations between the QUANTIDD score and hs-CRP appear to be robust. Finally, since the distribution of hs-CRP concentration was skewed, and the range of concentration of hs-CRP was narrow, in the present study, we compared hs-CRP concentrations between two QUANTIDD score groups. Therefore, we could not assess the trend between dietary diversity and hs-CRP concentration.

In conclusion, the results of this study suggest that a higher dietary diversity score might reduce the hs-CRP concentrations in Japanese male workers. Further larger longitudinal studies are needed to confirm this finding.

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**Data availability** The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate** The study was conducted according to the ethical standards of the Declaration of Helsinki, and the protocol was approved by the institutional review board of Tokushima University Hospital (ethical approval No. 2868). Written consent was obtained from all participants.

**Conflict of interest** All authors state that they have no conflicts of interest.

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