To evaluate each participant's habitual dietary patterns, the 10 food groups mentioned above were selected from the 15 original food groups, excluding the 5 food groups that include traditionally eaten staples (e.g., rice, miso soup, pickled vegetables, bread, and noodles) [18]. The questionnaire included examples of specific foods for each category to assist with appropriate selection of the food groups by the interviewers and participants. Examples of seafood included raw fish and all kinds of fish or clam products. The meat category included meat and all meat products. Eggs included chicken or quail eggs but not fish spawn. Milk included only pure milk, excluding milk flavored with coffee or fruit. Soy products were foods made from soybeans, such as tofu and *natto*, which is a traditional Japanese food made of fermented soybeans. Green and yellow vegetables were explained as vegetables that have dark colors, including carrot, spinach, pumpkin, and tomato. The seaweed category included both raw and dried products. Because it was determined that the potato category obviously consisted of white potato, sweet potato, and taro—all of which are consumed by Japanese people—a detailed explanation was not provided. Fruits included all fruits, both fresh and canned. Tomatoes were specified as vegetables, because some Japanese people consider them fruits. Oils and fats included butter, margarine, and all other kinds of oils used for cooking.

While some of the questions were multiple choice (5 response options at most), the responses for all variables were dichotomized for the analysis to ensure that the numbers of positive and negative responders were as similar as possible based on the baseline data. The thresholds based on the baseline data between positive and negative responses were also applied to the follow-up data. "Frequency of going out" had 4 response options (at least once/day, once/2–3 days, once/week, and very rarely), and the participants were classified as "once/2–3 days or less" or "at least once/day" for analysis. Responses to the questions about "strolling or light exercise" and "frequency of participating in such activities/week" were classified as "at least 2–4 days/week" or "once/week or less" for strolling and "at least 5–6 days/week" or "2–4 days/week or less" for light exercise. Regarding the question about "regular exercise and sports," participants were classified as "yes" or "no." Participants had 4 response options (almost every day, once/2 days, once or twice/week, or almost never) for the questions on the intake frequency of each food group and were ultimately classified as "once or twice/week or less" or "at least once/2 days" for meat and eggs and "once/2 days or less" or "almost every day" for all other food groups. The Dietary Variety Score (DVS), which is an index of dietary variety introduced by Kumagai et al. [19], was calculated by summing the number of times each participant answered "almost every day" for the intake of each of the 10 food groups [18–20]. The total score ranges from 0 (consuming once/2 days or less for all of the food groups) to 10 (consuming almost every day for all of the food groups). The women were then classified as "DVS $\leq$5" or "DVS $\geq$6." For "alcohol consumption" and "smoking habit," the participants were classified as "current drinker/smoker" or "non-drinker (never or ex-drinker)/non-smoker (never or ex-smoker)." The response options for the history of the previously listed diseases were "no history" or "with history." Participants who had a history of a disease were also asked about the current disease status; participants were ultimately classified as "currently negative" or "currently positive."

Statistical analysis

Somatometric parameters and KES are presented as population means ± standard deviations. Changes of these parametric variables over 4 years were examined using paired *t*-tests. The population status of each lifestyle-related variable is presented as the number of positive/negative responses. The statistical significance of changes in the ratios of these non-parametric variables was examined using the McNemar test.

A cross-sectional analysis was conducted to examine the relationships between the lifestyle-related variables and KES at baseline in the 575 women who also participated in the follow-up survey. For each lifestyle-related variable, we compared KES between those with positive and negative responses at baseline by using ANCOVA adjusted for baseline age and current status of all diseases, with each disease included as a separate variable.

We also conducted a longitudinal analysis to examine the associations between baseline lifestyle-related variables and changes in KES over 4 years. For each variable, we compared the changes in KES between those with positive and negative responses at baseline by using ANCOVA adjusted for baseline age, KES, and the status of all diseases, with each disease included as a separate variable.

All statistical analyses were conducted using PASW Statistics 18 (IBM Corp., Armonk, NY, USA). The results were regarded statistically significant when the *P*-value was <0.05.

Results

Participant characteristics at baseline and follow-up

The age of the 575 participants ranged between 75 and 85 years (78.07 ± 2.56) in 2008 and between 78 and 89 years (82.07 ± 2.55) in 2012 (Table 1). At baseline, the participants who did not return for the 2012 check-up were significantly older (78.86 ± 2.74 versus 78.07 ± 2.56 years, respectively) and had lower KES (192.36 ± 48.60 versus 205.95 ± 53.36 N, respectively) than those who returned. Both average the height and weight of the 575 final study participants decreased significantly over the 4 years of the study ($P < 0.001$, Table 1). No changes in body mass index or %body fat were observed. KES decreased significantly by approximately 10% over the course of 4 years.

The data for physical activities and other lifestyle factors showed that the participants generally became less active 4 years after baseline (Table 1). The proportion of women who went out at least once/day or participated in regular exercise and sports decreased significantly ($P < 0.001$, $P = 0.007$, respectively). The proportions of women who drank alcohol or smoked decreased by 4.2% and 1.2%, respectively (Table 1).

Regarding intakes of the different food groups, the proportion of women who consumed some of the food groups (i.e., meats, and oils and fats) more frequently (≥once per 2 days for meat and eggs, almost every day for other food groups) increased significantly over the course of 4 years (Table 1). The proportion of participants who ate meat at least once/2 days increased significantly by 5.7% (from 59.3% at baseline to 65.0% at follow-up; $P = 0.011$). The proportion of those who ate oils and fats almost every day increased significantly by 9.4% (50.6–60.0%; $P = 0.039$). In contrast, the proportions of women who ate soy products, green or yellow vegetables, seaweed, or fruits almost every day decreased significantly (all $P < 0.05$; Table 1). The proportions of women who had hypertension, osteoporosis, anemia, or gonarthrosis increased significantly over the 4 years (all $P < 0.05$; Table 1).

Cross-sectional analysis of knee extension strength at baseline

Cross-sectional analysis of the baseline data showed that some factors related to physical activity were significantly associated with KES at baseline (Table 2). The mean KES was higher in those who went out once/day or more or participated in regular exercise and sports than those who did not. We found no significant relationship between KES and other lifestyle-related factors including the frequency of walking, frequency of food intake of the studied food groups, DVS, alcohol intake, and smoking (Table 2).

Longitudinal analysis of the effects of lifestyle-related factors on knee extension strength

Longitudinal analysis showed that except for 3 food groups, no lifestyle-related variables at baseline were related to changes in KES over 4 years (Table 3). Those who ate seafood almost

Table 1. Subjects' characteristics at baseline and follow-up at 4 years (n = 575).

Variables	Baseline		Follow-Up		P-Value
	Mean	SD	Mean	SD	
Measured values					
Age	78.07	±2.56	82.07	±2.55	
Height, cm	148.42	±5.29	147.32	±5.50	P<0.001
Weight, kg	50.20	±7.89	49.33	±8.18	P<0.001
Body mass index, kg/m^2	22.78	±3.34	22.72	±3.53	0.286
%Body fat	31.94	±4.71	32.07	±7.74	0.528
Knee extension strength, N	205.95	±53.36	186.01	±54.60	P<0.001
	n	(%)	n	(%)	
Physical activities					
Going out (at least once per day)	472	(82.1)	419	(72.9)	P<0.001
Going for a stroll (at least 2–4days per week)	343	(59.7)	371	(64.5)	0.054
Light exercises (at least 5–6days per week)	287	(49.9)	314	(54.6)	0.060
Regular exercises and sports (Yes)	234	(40.7)	201	(35.0)	0.007
Foods & discretionary items					
Seafood (almost every day)	260	(45.2)	238	(41.4)	0.132
Meat (at least once per 2 days)	341	(59.3)	374	(65.0)	0.011
Egg (at least once per 2 days)	369	(64.2)	393	(68.3)	0.071
Milk (almost every day)	357	(62.1)	368	(64.0)	0.375
Soy products (almost every day)	395	(68.7)	358	(62.3)	0.006
Green and yellow vegetables (almost every day)	507	(88.3)	483	(84.0)	0.021
Seaweeds (almost every day)	314	(54.6)	252	(43.8)	P<0.001
Potatoes (almost every day)	248	(43.1)	211	(36.7)	0.326
Fruits (almost every day)	500	(87.0)	487	(84.7)	0.006
Oils and fats (almost every day)	291	(50.6)	345	(60.0)	0.039
Dietary variety score (≥6 points)	290	(50.5)	267	(46.4)	0.073
Drinking (Current drinker)	149	(25.9)	125	(21.7)	0.006
Smoking (Smoker)	22	(3.8)	15	(2.6)	0.039
Diseases					
Hypertension (positive)	306	(53.2)	365	(63.5)	P<0.001
Stroke (positive)	27	(4.7)	36	(6.3)	0.124
Heart disease (positive)	106	(18.4)	123	(21.4)	0.075
Diabetes mellitus (positive)	46	(8.0)	48	(8.3)	0.791
Hyperlipidemia (positive)	225	(39.1)	246	(42.9)	0.083
Osteoporosis (positive)	160	(27.8)	215	(37.5)	P<0.001
Anemia (positive)	10	(1.7)	21	(3.7)	0.043
Asthma (positive)	18	(3.1)	23	(4.0)	0.267
COPD (positive)	1	(0.2)	3	(0.5)	0.625
Osteoarthritis of hip (positive)	11	(1.9)	18	(3.1)	0.143
Gonarthritis (positive)	126	(22.0)	156	(27.1)	0.005

SD = standard deviation, COPD = chronic obstructive pulmonary disease, P-Values were outcomes of paired t-tests for continuous variables, and of McNemar tests for binary variables.

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Table 2. Result of the cross-sectional analysis showing the average knee extension strength according to binarized baseline lifestyle factors.

	Mean	SE	P-Value
Physical activities			
Going out			
Once per 2–3days or less (N = 98)	191.09	(5.24)	
At least once per day (N = 448)	209.62	(2.44)	.001
Going for a stroll			
1day per week or less (N = 214)	205.52	(3.56)	
At least 2–4days per week (N = 332)	206.77	(2.86)	.784
Light exercises			
2–4days per week or less (N = 272)	201.54	(3.15)	
At least 5–6days per week (N = 274)	211.02	(3.15)	.035
Regular exercises and sports			
No (N = 322)	199.99	(2.89)	
Yes (N = 224)	215.26	(3.47)	.001
Foods & discretionary items			
Seafood			
Once per 2 days or less (N = 299)	204.98	(3.01)	
Almost every day (N = 247)	207.87	(3.32)	.521
Meat			
1–2 times per week or less (N = 228)	203.31	(3.46)	
At least once per 2 days (N = 318)	208.41	(2.92)	.263
Egg			
1–2 times per week or less (N = 197)	200.51	(3.73)	
At least once per 2 days (N = 349)	209.55	(2.79)	.055
Milk			
Once per 2 days or less (N = 204)	203.45	(3.67)	
Almost every day (N = 342)	207.96	(2.82)	.333
Soy products			
Once per 2 days or less (N = 173)	201.72	(3.98)	
Almost every day (N = 373)	208.39	(2.69)	.168
Green and yellow vegetables			
Once per 2 days or less (N = 66)	203.52	(6.43)	
Almost every day (N = 479)	206.64	(2.38)	.650
Seaweeds			
Once per 2 days or less (N = 248)		(3.31)	
Almost every day (N = 298)	209.31	(3.02)	.139
Potatoes			
Once per 2 days or less (N = 311)		(2.97)	
Almost every day (N = 235)	208.22	(3.43)	.457
Fruits			
Once per 2 days or less (N = 71)		(6.22)	
Almost every day (N = 475)	207.24	(2.38)	.270
Oils and fats			
Once per 2 days or less (N = 271)		(3.18)	
Almost every day (N = 275)	205.53	(3.15)	.736
Dietary variety score			
DVS $\leq$ 5 points (N = 269)	198.11	(2.07)	

(*Continued*)

Table 2. (*Continued*)

	Mean	SE	P-Value
DVS ≥ 6 points (N = 276)	199.17	(2.00)	.714
Drinking			
Non-drinker (N = 404)	204.08	(2.58)	
Current drinker (N = 142)	212.50	(4.37)	.099
Smoking			
Non-smoker (N = 525)		(2.26)	
Smoker (N = 21)	220.99	(11.41)	.189

SE; Standard Error, Analyses of covariance were applied incorporating baseline age, and baseline status of all the diseases (hypertension, stroke, heart disease, diabetes mellitus, hyperlipidemia, osteoporosis, anemia, asthma, chronic obstructive pulmonary disease, hip osteoarthritis, gonarthrosis) as covariates.

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every day had a significantly greater decrease (1.5 times) in KES (24.68 N) than those who ate seafood once/2 days or less (16.88 N) ($P = 0.022$). In contrast, the intake of soy products and green or yellow vegetables had a beneficial effect on KES. The decrease of KES in participants who ate soy products almost every day (17.87 N) was approximately 69% of that in those who ate soy products once/2 days or less (26.06 N) ($P = 0.026$), and the decrease of KES in participants who ate green or yellow vegetables almost every day (18.82 N) was approximately 60% of that in those who ate these vegetables once/2 days or less (31.46 N; $P = 0.015$; Table 3).

Discussion

We conducted both cross-sectional and longitudinal analyses of the factors associated with KES on a cohort of elderly women in Japan. However, the associations between lifestyle-related factors and KES were inconsistent between analyses. Our cross-sectional analysis showed that women who go out or exercise regularly had a higher KES than those who did not. However, these variables were not significantly associated with changes in KES in the longitudinal analysis. Therefore, the significant association between physical activity-related lifestyle variables and KES at baseline might merely reflect the fact that women with strong legs were able to perform physical activities with fewer limitations.

The intake frequencies of seafood, soy products, and green or yellow vegetables, which were not associated with KES at baseline, were associated with changes in KES over 4 years. The routine intake of seafood negatively affected KES, while those of soy products and green and yellow vegetables had beneficial effects. The apparent discrepancy between the results of the 2 analyses indicates that conducting a cross-sectional analysis alone is insufficient for investigating the influences of lifestyle-related factors on muscle strength.

We did not expect that variables found to be associated with KES in the cross-sectional analysis (i.e., going out, and regular exercise and sports) would not show associations in the longitudinal analysis. Several intervention studies have established that exercise is effective for maintaining or even increasing muscle strength in the elderly [21–23]. One possible reason why our data do not seem to support the effect of physical activities on muscle strength is that some participants did not maintain their baseline physical activity level. However, an additional comparison between those who reported consistently going out and those who consistently reported not going out yielded no significant association with a change in KES (P = 0.307; data not shown). Therefore, the consistency of physical activity does not seem to be critical for maintaining muscle strength among elderly women. Although our study failed to

Table 3. Result of the longitudinal analysis showing the effect of baseline lifestyle factors on decline in muscle strength.

	Mean	SE	P-Value
Physical activities			
Going out			
Once per 2–3days or less (N = 95)	-19.87	(4.05)	
At least once per day (N = 439)	-20.51	(1.86)	.886
Going for a stroll			
1day per week or less (N = 207)	-22.53	(2.70)	
At least 2–4days per week (N = 327)	-19.04	(2.15)	.314
Light exercises			
≤2–4days per week (N = 266)	-19.94	(2.39)	
At least 5–6days per week (N = 268)	-20.86	(2.39)	.787
Regular exercises and sports			
No (N = 314)	-21.61	(2.22)	
Yes (N = 220)	-18.67	(2.66)	.404
Foods & discretionary items			
Seafood			
Once per 2 days or less (N = 292)	-16.88	(2.26)	
Almost every day (N = 242)	-24.68	(2.50)	.022
Meat			
1–2 times per week or less (N = 223)	-18.88	(2.62)	
At least once per 2 days (N = 311)	-21.48	(2.21)	.451
Egg			
1–2 times per week or less (N = 192)	-19.37	(2.84)	
At least once per 2 days (N = 342)	-20.98	(2.12)	.654
Milk			
Once per 2 days or less (N = 199)	-22.31	(2.78)	
Almost every day (N = 335)	-19.26	(2.13)	.388
Soy products			
Once per 2 days or less (N = 165)	-26.06	(3.04)	
Almost every day (N = 369)	-17.87	(2.02)	.026
Green and yellow vegetables			
Once per 2 days or less (N = 64)	-31.46	(4.85)	
Almost every day (N = 469)	-18.82	(1.78)	.015
Seaweeds			
Once per 2 days or less (N = 240)		(2.52)	
Almost every day (N = 294)	-18.10	(2.27)	.135
Potatoes			
Once per 2 days or less (N = 302)		(2.25)	
Almost every day (N = 232)	-18.08	(2.57)	.237
Fruits			
Once per 2 days or less (N = 70)		(4.68)	
Almost every day (N = 464)	-19.18	(1.80)	.068
Oils and fats			
Once per 2 days or less (N = 264)		(2.41)	
Almost every day (N = 270)	-22.30	(2.37)	.256
Dietary variety score			
DVS ≤5 points (N = 261)	-22.73	(2.42)	

(*Continued*)

Table 3. (*Continued*)

	Mean	SE	P-Value
DVS ≥6 points (N = 272)	-18.06	(2.37)	.171
Drinking			
Non-drinker (N = 395)	-20.06	(1.96)	
Current drinker (N = 139)	-21.33	(3.31)	.742
Smoking			
Non-smoker (N = 514)	-20.25	(1.71)	
Smoker (N = 20)	-24.14	(8.77)	.664

SE; Standard Error, Analyses of covariance were applied incorporating baseline age, baseline knee extensor strength, and baseline status of all the diseases (hypertension, stroke, heart disease, diabetes mellitus, hyperlipidemia, osteoporosis, anemia, asthma, chronic obstructive pulmonary disease, hip osteoarthritis, and gonarthrosis) as covariates.

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find an association of regular physical activity with KES, the beneficial effect of exercise on muscle strength cannot be denied.

The decline in KES was greater in women who ate seafood almost every day at baseline. However, this result may not be very robust, because the KES at baseline was slightly higher in women who ate seafood almost every day. Several studies indicate that regular seafood intake contributes to maintaining muscle strength [12,24,25]. For example, a cross-sectional study in the UK shows that fatty fish consumption positively influences grip strength in older people [12]. Rats fed Alaska pollock protein exhibit greater fast-twitch muscle hypertrophy than rats fed casein [24]. In a study conducted in older people, leg extension power was positively associated with the serum concentration of an active vitamin D derivative, which is abundant in seafood [25]. However, methyl mercury, a compound found in seafood, might negatively affect muscle strength. Accordingly, frequent intake of seafood with high levels of mercury in coastal villages is associated with a risk of toxicity, including weakened muscles [26,27]. However, because our study was conducted in Tokyo where no such cases have been reported, seafood intake does not seem to have affected muscle strength. Therefore, a study with a larger cohort seems necessary to clarify the effect of daily seafood intake on muscle strength.

The 4-year decline in KES was smaller in those who ate soy products almost every day than those who ate soy products once/2 days or less. Although we could not find direct evidence supporting the beneficial effect of soy products on muscle health in the literature, several studies suggest that some ingredients found in soy products, such as vitamin K_2 and isoflavone, improve bone metabolism [16–14,28]. In a study of 4 groups of participants eating different amounts of *natto* (rich in vitamin K_2) for 1 year, the risk of a reduction in bone formation markers in the group that ate *natto* most frequently was 0.07 times of that in the group that ate no *natto* [14]. Another prospective study of middle-aged Japanese women shows that 24 weeks of soy isoflavone supplementation increases bone mineral density [15]. A placebo-controlled study shows that menopausal women treated with isoflavone tablets exhibited a significant decrease in urinary excretion of urinary deoxypyridinoline, a specific biomarker of bone resorption [16]. An analysis of the association of regional differences in *natto* intake and hip fracture incidence revealed that fractures are less prevalent in regions where *natto* consumption is prevalent due to local culture [28]. The daily intake of soy products in our study may have contributed to the maintenance of muscle strength through a reduction of the incidence of fractures and resulting inactivity.

However, the questionnaire items about food intake used in the present study were not detailed enough to establish concrete data about the dietary habits of elderly people. Because our study was based on a retrospective analysis of existing data, we were unable to use very detailed questions. Therefore, studies using more detailed items about food intake aiming to understand how dietary habits affect elderly people's muscle strength seem necessary to make suggestions regarding the diet of elderly people for maintaining muscle strength.

The smaller decline of KES in women who ate green or yellow vegetables almost every day may be explained by the antioxidant effects of carotenoids and vitamin C. Recent epidemiological studies in community-dwelling elderly show that low serum concentrations of carotenoids or vitamin C are associated with low muscle strength [4,6,29–31]. A cross-sectional study revealed that daily dietary intake of vitamin C and β-carotene is significantly associated with KES [6]. A longitudinal observational study of people >64 years old further shows that those in the lowest quartile of total plasma carotenoid level have a significantly higher risk of muscle weakening 6 years later than those in the highest quartile [5]. Concordant with these studies, the present study corroborates the beneficial effect of the daily intake of green or yellow vegetables on age-related decline in muscle strength.

Contrary to our expectation, the intake frequency of meat at baseline did not influence changes in muscular strength. In a study of 1,844 Japanese senior citizens, those with the lowest initial density of serum albumin, which is processed from other proteins within the human body, had the highest incidence of ADL disability 12 years later [32]. In contrast, a longitudinal study in healthy aged men suggests that a low albumin concentration does not predict a decline in muscle strength [33]. Furthermore, a low baseline concentration of serum albumin failed to predict a decline in grip strength over 2 years in a study of frail elderly participants [34]. Another longitudinal study in Japanese elderly shows that a higher intake frequency of animal protein is associated with a lower risk of decline in functional capacity only in men [35]. As the association between protein intake and muscle health remains controversial, more cohort studies are needed to elucidate how meat intake affects muscle strength in the elderly.

This study has several limitations. First, we could not determine the amounts of each food consumed at the time of the baseline survey; instead, the questionnaire collected information about the number of days in a week that a given food was eaten. Nevertheless, we expect that the results of the questionnaire are at least generally related with the actual amounts of food eaten. Second, the data regarding lifestyle factors were only based on the answers to questions at a single time point. Therefore, it is uncertain whether a particular subject kept eating soy products, for example, at the same frequency for 4 years. Third, the data about physical activity levels were collected by interview. Although an objective measurement of physical activity is more appropriate for evaluating lifestyle, the retrospective design forced us to use the data obtained through the interviews.

In conclusion, the cross-sectional and longitudinal analyses yielded inconsistent results regarding the associations of lifestyle-related factors with KES. This inconsistency suggests that conducting both types of analyses is crucial. Because our study demonstrated that the age-related decline in muscle strength was lower in those who frequently ate soy products or green and yellow vegetables, recommending higher intakes of these foods might be a useful measure for protecting the muscle health of the elderly.

Supporting Information

S1 Dataset. Dataset containing all relevant data of the participants in 2008 and 2012.
(XLSX)

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Author Contributions

Conceived and designed the experiments: NK. Performed the experiments: NK MK KS HY YY HH SO HS TS HK. Analyzed the data: NK HK. Wrote the paper: NK.

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One-Year Change in the Japanese Version of the Montreal Cognitive Assessment Performance and Related Predictors in Community-Dwelling Older Adults

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OBJECTIVES: To examine the distribution and associated predictors of 1-year changes in the Japanese version of the Montreal Cognitive Assessment (MoCA-J) in community-dwelling older adults.

DESIGN: Prospective cohort study.

SETTING: Population-based cohort study in Tokyo, Japan.

PARTICIPANTS: Individuals aged 65 to 84 (N = 496).

MEASUREMENTS: Multinomial logistic regression analysis was performed to estimate the odds of experiencing subsequent improvement in MoCA-J performance, as opposed to stable or deteriorating, while simultaneously adjusting for baseline MoCA-J score and major confounders.

RESULTS: Mean age was 74.0 ± 4.8; mean MoCA-J score was 23.7 ± 3.6. Only 40% had stable MoCA-J performance; 30% experienced deterioration and 30% improvement. Age increment, hospitalization in previous year, slower Timed Up and Go (TUG) score, and slower maximum walking speed were predictive of subsequent MoCA-J performance deterioration.

CONCLUSION: Slower TUG and walking speed performances were independent predictors of short-term MoCA-J deterioration. Research aimed at assessing lower-extremity performance-based tests in MCI-related decision-making is warranted. **J Am Geriatr Soc 63:1874–1879, 2015.**

Key words: Montreal Cognitive Assessment Japanese version; predictors; community-dwelling; older adult; prospective study

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Cognitive decline is a major clinical and public health concern that threatens the quality of life of older adults and their families and poses significant challenges to aging societies. Intensive research has increased knowledge about the epidemiology of the heterogeneous cognitive decline process with advancing age, including the characterization of prevalent disorders in older adults who do not meet the criteria for dementia but have clinically meaningful cognitive impairment such as mild cognitive impairment (MCI).[1] Knowledge about what constitutes accelerated cognitive decline over time in older adults and related risk factors nonetheless remains to be better characterized. Such knowledge could be useful in expanding the conceptualization and characterization of cognitive vulnerability in older adults living in the community by incorporating information on longitudinal changes in cognitive decline as a complement to the prevalent indices of cognitive status. The identification of older adults experiencing accelerated cognitive decline could also be an important preliminary step in the design and assessment of novel clinical and public health approaches.

The Montreal Cognitive Assessment (MoCA)[2] is a screening tool that has been validated in many different countries,[3] including Japan.[4] It has been traditionally useful in the clinical setting for the detection of prevalent cognitive impairment in older adults with MCI or early dementia. The MoCA may also be used for evaluation of changes in cognitive function over time in the clinical setting. For example, in a recent 2-year longitudinal observational study of older Japanese adults attending an outpatient memory clinic, the Japanese version of the MoCA test (MoCA-J), was shown to capture cognitive decline over a 2-year period in older adults with MCI and early-stage Alzheimer's disease (AD),[5] but less is known about the usefulness of MoCA scores in evaluating time-course changes in cognitive function in older adults in population-based settings.

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With this background, the current study was designed to examine the distribution and associated predictors of short-term changes in MoCA-J performance, as assessed according to within-individual differences in scores obtained in two visits conducted 1 year apart in a population-based epidemiological study of community-dwelling older adults living in Tokyo, Japan.

METHODS

Study Area and Participants

This study was conducted in Itabashi ward, northwest Tokyo, Japan. All participants were registered residents aged 65 to 84 living in nine residential areas surrounding the Tokyo Metropolitan Institute of Gerontology (TMIG). After exclusion of those who were institutionalized or participating in other research studies, invitations to participate in the study's comprehensive baseline health assessment were sent to 6,699 people, of whom 904 community-dwelling, ambulatory older adults independent in activities of daily living (ADLs) were enrolled and attended the study's baseline visit at TMIG in 2011. A follow-up assessment, which used methods and procedures similar to those used in the baseline, was conducted with 496 participants at TMIG in 2012. All subjects provided written informed consent to participate in the study, which the institutional review board and ethic committee of the TMIG approved (acceptance 5, 1, 2011).

Cognitive Function

Trained research assistants assessed each participant's cognitive functioning using the MoCA-J[4] and the Mini-Mental State Examination (MMSE).[6] MoCA-J and MMSE scores range from 0 to 30, with higher scores indicating better cognitive performance. MoCA-J was selected a priori as the study's main cognitive test, given its greater sensitivity in the detection of MCI in community-dwelling older adults than the MMSE.[4]

Conceptually, the outcome of interest was clinically meaningful short-term decline in MoCA-J performance, although there is no currently accepted standard measure of meaningful decline in MoCA-J score, as a literature review indicated. In this context, taking into account the available data, and consistent with the literature,[7] meaningful within-individual decline in MoCA-J performance was operationally defined as a decrease of two or more points in test scores obtained 1 year apart. Participants whose baseline and 1-year follow-up scored did not differ by more than one point were classified as having stable MoCA-J, and improvement of two or more points was classified as performance improvement.

Physical Performance

Usual and maximum walking speeds were calculated as the time required to walk 10 m on a 16-m straight and flat walkway at the participants self-selected and rapid paces. Handgrip strength was evaluated using a mechanical dynamometer in the dominant hand. For the Timed Up and Go (TUG) test, participants were instructed to stand up from a chair, walk forward to a 3-m marker, turn, walk back to the chair, and sit down as fast as possible. The time was recorded in seconds. Two trials were conducted per person, with the shorter time used in the analysis.

Other Variables

Questions were asked in standardized fashion using an interview survey comprising a wide range of health-related variables listed in Stuck's review[8] on risk factors for functional decline in older adults, including sociodemographic variables (age, sex, years of education); self-reported general and psychological variables such as self-rated health and depressive burden symptoms assessed using the Self-Rating Depression Scale,[9,10] a screening tool based on the sum of scores of 20 items, with each item scored as 1 or 4 with possible scores ranging from 20 to 80 and scores over 60 indicating moderate to severe depressive symptoms; and medical variables regarding diseases and hospitalization, including self-report of hospitalization in the previous year, medication use, prevalent chronic medical conditions (hypertension, stroke, heart disease, diabetes mellitus), and long-term care insurance certification.

Interviews also included a functional capacity assessment. Participants were asked about ability to perform ADLs. Instrumental activities of daily living were assessed as part of the TMIG Index of Competence.[11,12] The response to each item was scored 1 for yes and 0 for no. Higher scores indicate higher levels of competence. Health habits and social activities were assessed. Participants were asked how often they participated in sports or exercised. Smoking and alcohol consumption were also assessed.

Information was collected on vital signs and clinical laboratory data. Body mass index was calculated using height and body weight. Heart rate and blood pressure were measured with the participant seated and after 5 minutes of rest. Nonfasting blood samples were collected while participants were seated.

Statistical Analysis

Distribution of baseline characteristics of study subjects according to categories indicative of change in MoCA-J performance from baseline to the 1-year follow-up visit were examined using *t*-tests or the Mann–Whitney *U*-test for continuous variables and the chi-square test or Fisher exact test (when the expected number was <5) for categorical variables.

Multinomial logistic regression analysis was the primary analytical tool. It was used to estimate the odds of experiencing subsequent improvement in MoCA-J performance, as opposed to stable or deterioration, while simultaneously adjusting for baseline MoCA-J score and major confounders, including age, sex, education, self-rated health, history of hospitalization in the previous year, number of chronic diseases, and positive screening for depression. Confounding variables listed above were selected a priori on the basis of clinical considerations to minimize confounding effects from demographic characteristics and traditional indicators of disease and health status. The possibility of considering additional measures as meaningful potential confounders based on the analysis

displayed in Table 1 was also allowed for, but no other variable was included because of lack of statistical significance. All statistical analyses were conducted using SPSS/PC+ statistical software for Windows version 20.0 (SPSS, Inc., Chicago, IL). *P*-values were two-tailed, and the level of significance was set at .05.

Table 1. Baseline Characteristics of Study Participants[a] and Their Association with Change in Performance on the Japanese Version of Montreal Cognitive Assessment (MoCA-J) (2011–2012)

Characteristic	Deterioration, n = 147[b]	Stable, n = 202[c]	Improvement, n = 147[d]	*P*-Value[e]
Sociodemographic				
Age, mean ± SD	74.0 ± 4.8	72.4 ± 4.5	72.8 ± 4.9	.01
Female, %	55.8	57.4	60.5	.70
Education, year, mean ± SD	12.4 ± 2.8	12.6 ± 2.6	12.8 ± 2.9	.39
Cognitive function performance at baseline survey in 2011				
Mini-Mental State Examination score, median (IQR)	28.0 (27–29)	28.0 (27–29)	28.0 (25–30)	.20
MoCA-J score, mean ± SD	24.4 ± 3.5	24.2 ± 3.7	22.3 ± 3.1	<.001
MoCA-J, median (IQR)	25.0 (22–27)	22.0 (21–24)	22.0 (17–27)	<.001
Physical function performance				
Grip strength, kg, mean ± SD	25.6 ± 7.5	26.6 ± 8.0	26.4 ± 8.4	.49
Maximum walking speed, k/s, mean ± SD	1.8 ± 0.3	1.9 ± 0.4	1.9 ± 0.3	.09
Usual walking speed, m/s, mean ± SD	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	.71
Timed Up and Go test, seconds, mean ± SD	6.5 ± 1.8	6.3 ± 1.8	6.0 ± 1.2	.049
Functional status assessed according to IADL of TMIG-IC score, mean ± SD (range 0–5)	5.0 ± 0.3	5.0 ± 0.1	4.9 ± 0.3	.43
Self-reported general and psychological health, %				
Fair or poor health	20.4	13.9	18.4	.25
Moderate to severe depression	7.5	5.4	6.8	.73
Diseases and hospitalization, %				
Hospitalization in previous year	15.0	9.9	7.5	.10
History of hypertension	40.8	47.5	35.4	.07
History of stroke	2.7	7.9	4.8	.10
History of heart disease	18.4	16.3	15.6	.81
History of diabetes	15.0	12.9	11.6	.68
Number of chronic conditions, mean ± SD (range 0–4)	0.8 ± 0.8	0.8 ± 0.9	67.4 ± 0.8	.16
Health habits and social activities, %				
Sports or exercise	31.3	38.6	34.0	.35
Current smoker	5.4	8.5	12.9	.15
Current drinker	46.9	44.1	49.7	.73
Vital signs				
Systolic blood pressure, mmHg, mean ± SD	134.0 ± 17.0	132.0 ± 19.0	132.0 ± 20.0	.60
Diastolic blood pressure, mmHg, mean ± SD	76.1 ± 10.6	75.0 ± 11.1	75.8 ± 10.4	.56
Heart rate, beats/min	72.4 ± 11.2	72.6 ± 10.9	71.0 ± 11.0	.35
Body mass index, kg/m^2, %				
<18.5	8.2	6.4	8.2	.25
18.5–24.9	72.8	64.9	72.8	
25.0–29.9	15.6	25.7	15.6	
≥30.0	3.4	3.0	3.4	
Clinical laboratory				
Serum albumin, g/dL, mean ± SD	4.3 ± 0.2	4.3 ± 0.3	4.3 ± 0.2	.94
Glycosylated hemoglobin, %				
<5.1	35.6	37.3	41.5	.87
5.1–5.3	31.5	34.8	31.3	
5.4–5.6	15.1	11.4	11.6	
5.7–6.3	11.6	10.4	12.2	
>6.3	6.2	6.0	3.4	
Hemoglobin, g/dL, mean ± SD	13.3 ± 1.2	13.4 ± 1.3	13.4 ± 1.1	.62
Serum high-density lipoprotein cholesterol, mg/dL, mean ± SD	63.9 ± 16.8	62.9 ± 15.7	65.7 ± 17.4	.28
Serum low-density lipoprotein cholesterol, mg/dL, mean ± SD	116.5 ± 29.8	112.5 ± 28.9	114.2 ± 24.7	.44

SD = standard deviation; IQR = interquartile range; IADL = Instrumental Activity of Daily Living; TMIG-IC = Tokyo Metropolitan Institute of Gerontology-Index of Competence.

[a]1-year change in MoCA-J performance classification based on the difference between 2011 and 2012 MoCA-J scores. All of the participants were independent in activities of daily living.

[b]Decrement of ≥2 points in 1 year.

[c]Remaining within ±1 point of baseline score.

[d]Improvement of ≥2 or more points.

[e]*P*-values from chi-square tests or Fisher exact test (when the expected number was <5) for categorical variables and Mann–Whitney *U*-test for continuous variables.

RESULTS

The mean ± standard deviation age of study participants was 73.0 ± 4.7. Significant changes in MoCA-J score were observed between baseline and follow-up visits, which occurred 1 year apart (Figure 1). Only 40% of study participants had stable MoCA-J scores, which were defined as no change or a change of no more than ±1 point. Approximately 30% of participants had an increase in MoCA-J score of two or more points, and 30% had a decrease of two or more points at the follow-up visit. Of those with baseline MoCA-J scores of 22 or greater (n = 323), 19.8% dropped to scores of 21 or less—a threshold mainly characterized as having high specificity and positive predictive value for MCI.[4]

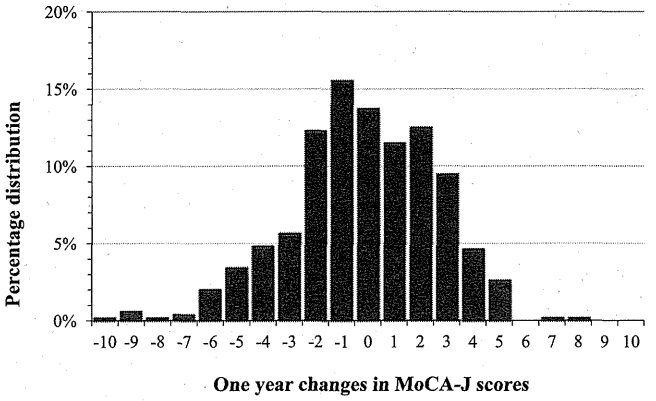

Figure 1. Percentage distribution of changes in the Japanese version of Montreal Cognitive Assessment (MoCA-J) scores over a 1-year period in community-dwelling older Japanese men and women, Itabashi Ward, Tokyo.

Crude bivariate analyses reported in Table 1 indicated that, of all measures considered, three were related to subsequent changes in MoCA-J scores between 2011 and 2012: age, baseline MoCA-J score, and TUG. Participants who experienced subsequent decline in MoCA-J performance were older than those who had stable or increases in MoCA-J scores (P = .01). Participants whose MoCA-J performance declined (24.4 ± 3.5) or remained stable (24.2 ± 3.7) had higher baseline MoCA-J scores than those whose performance improved (22.3 ± 3.1) (P < .001). A dose–response relationship was observed between TUG performance and MoCA-J change categories (P = .049), with the best, intermediate, and worst TUG performance observed at baseline related to subsequently improved, stable, and declined MoCA-J scores, respectively.

Table 2 displays results of multivariate multinomial logistic regression analyses. Older age, history of hospitalization in the previous year, and higher baseline MoCA-J score were associated with greater odds of subsequent decline than of improvement. Better performance on the TUG test was associated with greater odds of improved or stable scores than of worse MoCA-J performance at the follow-up visit, even after adjustment for demographic, baseline MoCA-J, and disease and health status variables included in Model 1. For example, the estimated adjusted odds of decline as opposed to improvement in MoCA-J performance in the follow-up visit was 1.45 (95% confidence interval = 1.19–1.78) times as high per 1 second longer on the TUG test. In Model 2, in which maximum walking speed was included as the physical performance measure in the model in replacement of the TUG, faster

Table 2. Multivariate Polytomous Logistic Regression Estimates of Likelihood of Decline or Remaining Stable, as Opposed to Improvement, in Japanese Version of Montreal Cognitive Assessment (MoCA-J) Performance in 1 Year (2011–2012)

	Decline vs Improvement	Stable vs Improvement
Model	**Odds Ratio (95% Confidence Interval) *P*-Value**	
1		
Age, 1-year increment	1.07 (1.01–1.14) .01	0.99 (0.94–1.05) .81
Male	1.52 (0.89–2.60) .12	1.46 (0.89–2.40) .13
Education, 1-year increment	0.91 (0.83–1.00) .05	0.93 (0.85–1.01) .09
Self-rated health poor or fair (vs excellent or good)	1.18 (0.60–2.34) .63	1.82 (0.94–3.55) .08
History of hospitalization in previous year	2.46 (1.04–5.78) .04	1.60 (0.68–0.27) .28
Number of chronic conditions, per increment of 1 disease (range 0–4)	1.01 (0.73–1.39) .96	1.26 (0.94–1.68) .12
Depressive mood moderate to severe (vs not or slightly)[a]	1.65 (0.61–4.49) .33	1.05 (0.39–2.80) .92
Timed Up and Go test, 1-second increment	1.45 (1.19–1.78) <.001	1.39 (1.14–1.68) .001
MoCA-J at baseline, 1-point increment	1.34 (1.22–1.46) <.001	1.26 (1.16–1.36) <.001
2		
Age, 1-year increment	1.07 (1.01–1.14) .02	0.99 (0.94–1.05) .82
Male	1.62 (0.93–2.81) .09	1.45 (0.87–2.42) .15
Education, 1-year increment	0.91 (0.83–1.00) .06	0.93 (0.85–1.01) .09
Self-rated health poor or fair (vs excellent or good)	1.07 (0.55–2.10) .84	1.57 (0.82–2.99) .17
History of hospitalization in previous year	2.56 (1.10–5.99) .03	1.63 (0.71–3.77) .25
Number of chronic conditions, per increment of 1 disease (range 0–4)	1.01 (0.73–1.39) .96	1.27 (0.96–1.70) .10
Depressive mood moderate to severe (vs not or slightly)[a]	1.50 (0.56–4.01) .42	1.03 (0.40–2.67) .95
Maximum walking speed, 1-m/s increment	0.27 (0.11–0.67) .004	0.42 (0.19–0.93) .03
MoCA-J at baseline, 1-year increment	1.30 (1.20–1.42) <.001	1.22 (1.13–1.31) <.001

[a]Depressive mood was assessed according to Self-Rated Depression Scale score ≥60 (moderate to severe) vs less than 60 (not or slightly depressed).

maximum walking speed was consistently associated with greater odds of decline than of improvement in MoCA-J performance at the follow-up visit.

DISCUSSION

The present study documented substantial heterogeneity in short-term MoCA-J score changes in community-dwelling older adults. Only 40% of participants had stable MoCA-J performance over a 1-year period, operationally defined here as no change or change of no more than ±1 point. Approximately 30% improved their MoCA-J scores by two or more points, and 30% had scores that were two or more points lower. Furthermore, of a comprehensive list of traditional clinical parameters and health and functional status indicators, only a few were associated with short-term changes in MoCA-J performance. These indicators objectively measure physical function performance such as TUG and maximum walking speed, as well as age and history of hospitalization in the previous year. Altogether, findings reported in this study offer a novel insight into the epidemiology of short-term decline in cognitive function in community-dwelling older populations with apparently preserved health.

Slower maximum walking speed and longer time on the TUG test were predictive of cognitive decline, as assessed according to MoCA-J score decline. TUG and maximum walking speed are well-established, objective tests of mobility performance. Several cross-sectional[13,14] and longitudinal[15–17] studies have shown that measures of physical and cognitive performance correlate with each other, even in older persons without apparent cognitive impairment. Although precise mechanisms controlling walking are not well understood, recent studies have presented evidence of relationships between age-related gait dysfunction and diffuse brain magnetic resonance imaging abnormalities such as morphological change in white matter hyperintensity.[18–20] Another study[21] reported that smaller left cerebellum and left prefrontal regions were associated with slower gait, independent of covariates and white matter hyperintensity. A recent study indicated that regional cerebral metabolic rates of glucose (rCMRglu) in the prefrontal cortex were associated with control of gait speed.[22] Another recent cross-sectional study reported that slower maximum walking speed was associated with lower rCMRglu in the prefrontal, posterior cingulate, and parietal cortices, independent of major health factors.[23]

Slower TUG performance independently predicted decline in MoCA-J score, consistent with cross-sectional results reported previously,[24] in a study that found that slower TUG time was independently associated with poorer global cognition, executive function, and memory. The current results highlight that TUG, in addition to its value as a mobility test, could potentially be used to provide insight into current cognitive abilities that are relevant for mobility functioning, as well as into the likelihood of subsequent cognitive decline in the short term in community-dwelling older adults.

The strengths of this study include its community setting and prospective design and the availability of a wide range of clinical, physical function, and cognitive data obtained in a standardized fashion. Important study limitations should also be acknowledged. First, the follow-up study was limited (1-year), limiting the degree of cognitive decline that could be observed in the community-dwelling older population studied. Nonetheless, the follow-up interval of 1 year is meaningful from a public health perspective. This is because every local government in Japan has conducted a brief geriatric screening that guides public health planning on an annual basis, considering that the Japan Ministry of Health, Labour and Welfare conducts assessments evaluating long-term care service needs for most elderly users every 6 to 12 months. To the knowledge of the authors, this is the first study to report data on short-term changes in MoCA test results in community-dwelling older adults and relevant predictors. Second, there is no accepted criterion to define what constitutes meaningful change in MoCA score over time in community-dwelling older adults, whether in Japan or elsewhere; nonetheless, expected observed associations between older age, recent hospitalization, and worse physical function performance and cognitive decline according to the operational definition used in this study offer convergent validity support. Third, because of limited follow-up and the availability of two test scores per person, this study could not provide insight into longer-term cognitive function and distal outcomes of those who experienced increase in MoCA-J score and may have transitioned from MCI to normal cognition.[25,26] It is possible that instability in MoCA-J scores could represent a transitional stage associated with greater rate of subsequent cognitive decline, but another hypothesis remains to be evaluated; although MoCA-J has a high test–retest reliability,[4] there is a possibility that the score changed because of learning effect.

In conclusion, MoCA-J scores may change significantly in community-dwelling older adults over a follow-up period of only 1 year, and MoCA-J changes may be clinically meaningful. Also, demographic characteristics (age), history of recent hospitalization, and simple physical performance tests (TUG, maximum walking speed) could be useful in predicting score decline. These findings enhance knowledge about the epidemiology of short-term cognitive decline in older adults living in the community, which could prove useful in the context of MCI-related public health planning.

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Original Article

Circadian Rhythm Affects the Dynamics of S-IgA Mucosal Secretion

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Abstract

Today, many people prefer the simplicity of eating at fast-food restaurants. The prevalence of overweight and obesity thus seems likely to continue to rise in coming decades, and recent evidence has demonstrated that obesity is associated with cancer, infectious diseases, and metabolic syndrome. We hypothesized that obesity induces mechanical changes in the digestive and circulatory organs, which may in turn disrupt homeostasis. This study investigated systemic and local impacts of diet-induced obesity on the immune system, including the mucosal tissues. Mice were administered a high-fat diet (HFD) or normal diet (ND) for 3 weeks, after which plasma and fecal extracts were collected at 6-h intervals. A significant reduction in plasma immunoglobulin (Ig) G and increase in fecal secretory (S-) S-IgA concentrations were observed in HFD-fed mice. In addition, corticosterone levels were significantly higher in the plasma of mice fed HFD when compared with those fed ND, indicating that daily intake of high-fat foods causes physiological stress. Taken together, these results suggest that regular consumption of high-fat foods may negatively impact both systemic and mucosal immune responses.

Keywords :
daily rhythm; S-IgA; high-fat diet

Introduction

Life on Earth is governed by circadian fluctuations in light intensity caused by the rotation of the planet around its own axis. Biological clocks are oscillator mechanisms that enable the anticipation of diurnal and nocturnal variations in environmental conditions, thereby coupling physiological processes to geophysical time(1). Circadian rhythms are daily changes or fluctuations in physiological processes and are regulated by numerous genes, the expression of which undergoes peaks and troughs at approximately 12-h intervals, with a full cycle covering 24 h.

Light and daily rhythms are thought to exert a strong influence on immune function(2). Several studies have described circadian variations in different immune parameters, such as lymphocyte proliferation, antigen presentation, and cytokine gene expression(3, 4). Many of these parameters, including circadian fluctuations in cytokine levels, are recapitulated in both mice and humans(5-7). For instance, several types of lymphocytes, including macrophages, dendritic cells, and B cells, express oscillations of molecular clock genes(8, 9).

Immunoglobulin (Ig) A, particularly secretory (S-) IgA, is the most abundant mucosal antibody isotype produced in the human body and plays an important role in maintaining intestinal homeostasis. S-IgA functions in a variety of ways to protect the vast mucosal surface of the body, such as the linings of the respiratory, gastrointestinal, and genitourinary tracts, as well as the oral cavity. These mucosal surfaces represent an enormous area of potential exposure to inhaled and ingested pathogens. S-IgA, as the major immunoglobulin present at these sites, can both prevent the attachment of microbial components to intestinal epithelial cells and also promote the clearance of microorganisms. These functions are important for the host, as they reduce the risk of infection and maintain an intestinal environment suitable for

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the appropriate commensal population(10).

The present study characterized circadian fluctuations in S-IgA production at mucosal surfaces in mice and examined the effects of daily diet on immune responses in mice. We provide evidence showing that mucosal production of S-IgA follows a circadian rhythm. We also found that regular intake of a high-fat diet (HFD) affects both fluctuations in immunoglobulin isotype production and total levels of antibody in mucosal secretions and plasma. These findings may prove useful in the development of new immunotherapies.

Materials and Methods

Mice

Female 7-week-old BALB/c mice were purchased from Sankyo Laboratory Service (Tokyo, Japan) and maintained under pathogen-free conditions in the experimental facility of Nihon University School of Dentistry at Matsudo. Mice were provided sterile food and water, maintained under constant environmental conditions, and entrained to a 12-h light/12-h dark cycle (light period from 07:00 to 19:00) for at least 2 weeks before experiments. Plasma and mucosal secretions (fecal extracts [FEs] and saliva) were collected every 6 h (i.e., at 07:00, 13:00, 19:00, 01:00, and 07:00, as these times correspond with Zeitgeber times [ZT] 0, 6, 12, 18, and 24, respectively). All animals were maintained and used in accordance with the Guidelines for the Care and Use of Laboratory Animals by Nihon University School of Dentistry at Matsudo (AP14MD003).

Induction of high-fat states

One week after of housing, mice were divided randomly into two groups (n = 6 per each time point, total n=30 per group). High fat diet (HFD)-fed group were given a HFD containing 16.5% fat, 22.6% protein and 45.1% carbohydrate (Oriental Yeast Co., Tokyo, Japan) for 3 weeks. Drink water was provided to mice *ab libitum*.

Sample collection

Samples of plasma and mucosal secretions (FEs and saliva) were collected from mice at 6-h intervals, as described above. Blood was collected into heparinized collection tubes by retro-orbital bleeding of anesthetized mice. The plasma was separated from cells by a 10-min centrifugation step at $10,000 \times g$(11). Saliva was obtained following interaperitoneal injection with 100 μg of sterile pilocarpine(12). Fecal pellets (100 mg) were suspended into 1 mL of phosphate-buffered saline (PBS) containing 0.1% sodium azide and were then extracted by vortexing for 5 min. The sample was centrifuged at $10,000 \times g$ for 5 min, and the supernatants were collected as FEs(12-14).

Isotype of immunoglobulins from systemic and mucosal secretions

Total levels of specific immunoglobulins in plasma and mucosal secretions were determined by enzyme-linked immunosorbant assay (ELISA). Briefly, 96-well Falcon microtest assay plates (BD Biosciences, Franklin, NJ) were coated with 5 μg/mL of total-Ig (H + L) in PBS. After blocking with 1% bovine serum albumin in PBS, 2-fold serial dilutions of samples were added and incubated overnight at 4 ℃. Horseradish peroxidase-labeled goat anti-mouse γ or α heavy chain-specific antibodies (Abs) (Southern Biotechnology Associates, Birmingham, AL) were then added to individual wells. The color reaction was allowed to developed for 15 min at room temperature with 100 μL of 1.1 mM 2.2'-azino-bis-(3-thylbenzthiazoline-6-sulfonic acid) in 0.1 M citrate phosphate buffer (pH 4.2) containing 0.01% H_2O_2. End-point titers were expressed as the reciprocal log2 of the last dilution that gave an Optical Density (O.D.) at 415 nm of 0.1 greater than background.

Corticosterone assay

To assess the adrenal response after given HFD for 3 weeks, the corticosterone concentration was measured using a commercial ELISA kit followed by manufacturer's guidelines (YK240, Yanaihara Institute Inc., Shizuoka Japan). The concentration of corticosterone in plasma samples was calculated from a standard curve and expressed in ng/ml.

Statistical analysis

Student's *t*-test (two-tailed) was used for all statistical analyses, and differences showing values $p<0.05$ were considered statistically significant.

Results

Circadian fluctuation in S-IgA levels in mucosal secretions

To characterize circadian changes in S-IgA Abs levels in mucosal secretions, we performed ELISA with FEs and saliva collected from mice every 6 h during daily light-dark cycles (Fig. 1). The level of S-IgA in FEs fluctuated over the

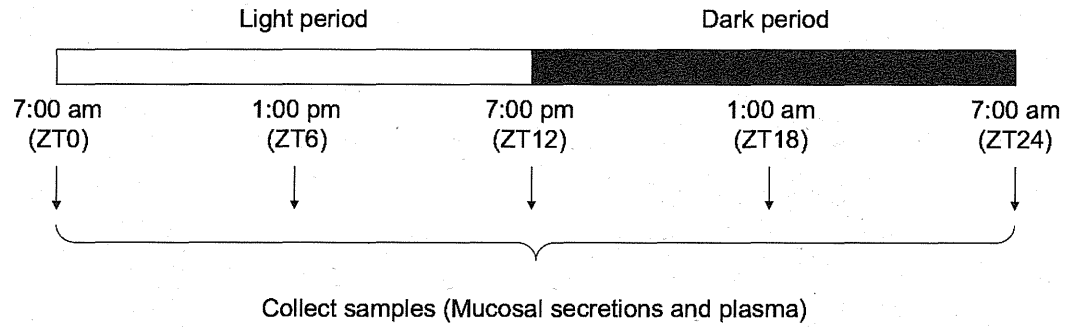

Fig. 1 Schematic showing sampling times of mucosal secretion (fecal extracts and saliva) and plasma during light and dark periods. All samples were collected every 6 hours (i.e., 7:00 am, 1:00 pm, 7:00 pm, 1:00 am, and 7:00 am) as there time correspond with Zeitgeber time [ZT] 0, 6, 12, 18, 24 respectively.

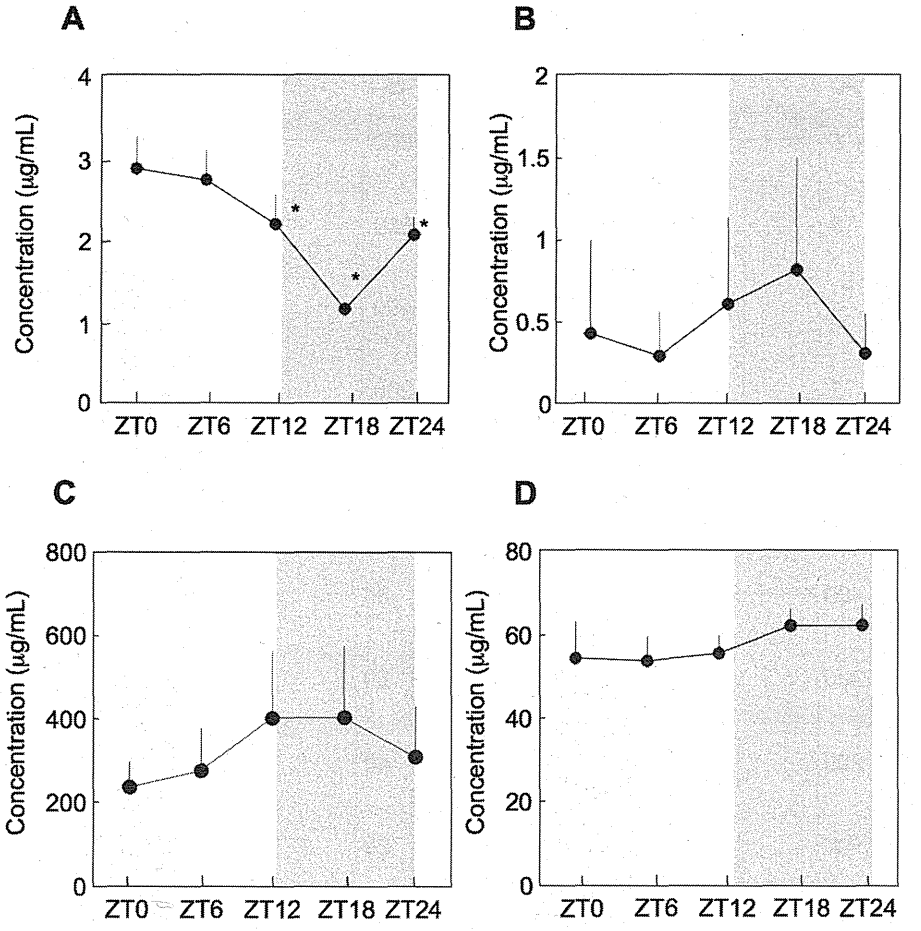

Fig. 2 Concentration of S-IgA in fecal extracts (A) or saliva (B), plasma IgG (C), and plasma IgA (D) concentrations in BALB/c mice. Concentrations of total IgG and IgA were determined over a 24 hr period by ELISA. Data are mean±SEM. n=6 mice per each time point. *$p<0.05$ vs ZT0.

course of the day (Fig. 2A), declining significantly at the midpoint of the dark cycles (i.e., ZT18). Furthermore, slight but daily fluctuations in S-IgA levels were also observed in saliva (Fig. 2B). We next analyzed whether these daily fluctuations also occurred in the plasma. A slight increase in plasma IgA level was observed during the dark period (ZT12-ZT24). Importantly, significant increases in IgG level were observed in the same dark period (Fig. 2C, D). Taken together, these results suggest that productions of both IgG and IgA fluctuate in a 24-h cycle. Interestingly, robust

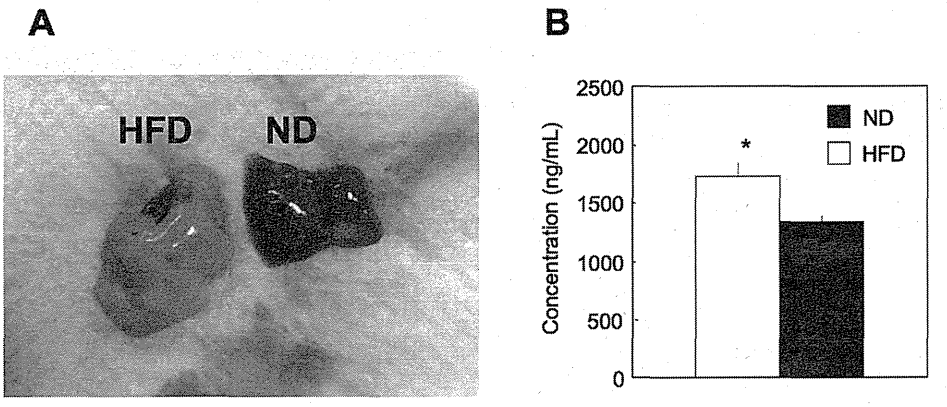

Fig. 3 Observation of condition of liver of mice fed with HFD for 3 weeks (A). Concentration of corticosterone in plasma of mice fed with HFD for 3 weeks (B). Data are mean±SEM. n=6 mice each group. * $p<0.05$ ND.

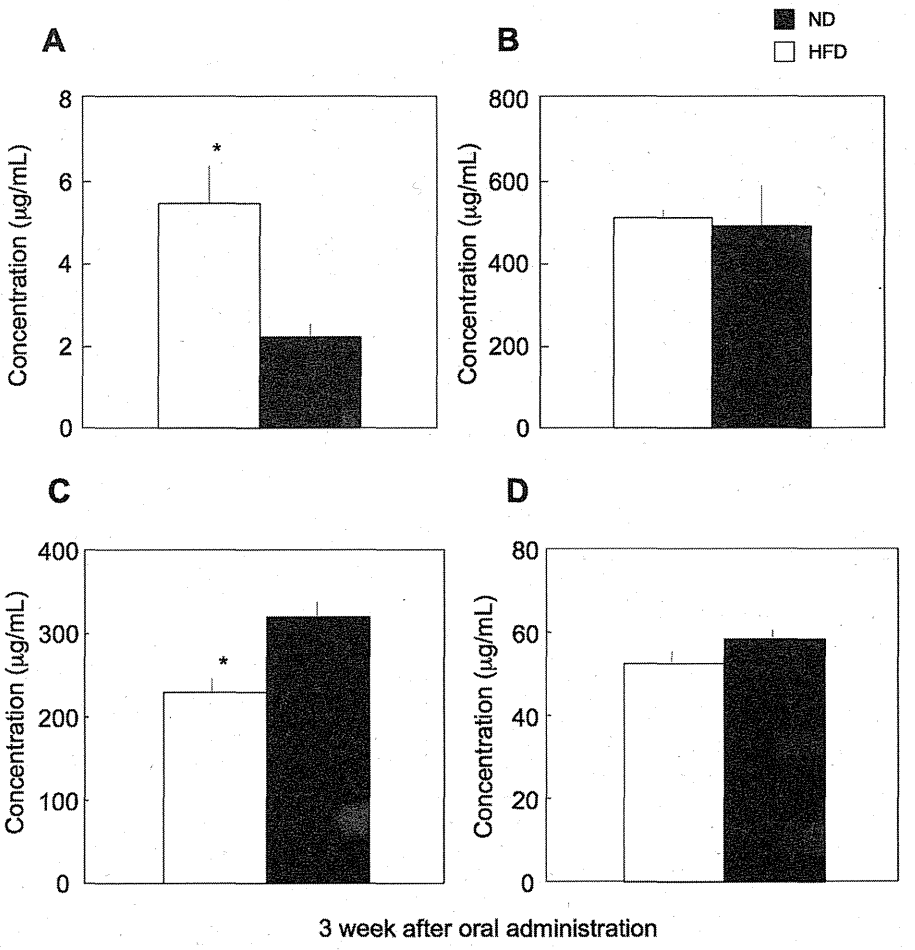

Fig. 4 Mean concentration of S-IgA in fecal extracts (A), Saliva (B), plasma IgG (C), and plasma IgA (D) in BALB/c mice fed a HFD or ND for 3 weeks. Data are mean±SEM. n=30 from ZT0, ZT6, ZT12, ZT18, and ZT24. * $p<0.05$ vs ND.

fluctuations in FEs were observed.

Feeding with HFD induced stress

Mice appeared healthy whether they were fed HFD or normal diet (ND). All HFD-fed mice showed slightly increased body weight when compared with the ND-fed mice group (data not shown). Importantly, hypertrophic and discolored liver was observed in HFD-fed mice (Fig.