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Cultural and life style practices associated with low inflammatory physiology in Japanese adults

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ABSTRACT

Japan is an exceptionally healthy East Asian country with extended longevity. In addition, the typical levels of several proinflammatory proteins, including both C-reactive protein (CRP) and interleukin-6 (IL-6), are often reported to be low when compared to American and European populations. This analysis determined if blood levels of CRP and IL-6 were associated with 4 cultural practices reflective of Japanese behavior and customs – drinking tea, eating seafood, consuming vegetables, and partaking in relaxing baths regularly – among 382 adults living in Tokyo. Regression models controlled for demographic factors, adiposity (BMI), physical exercise, smoking, alcohol use, and chronic illness (e.g., diabetes). Consuming a Japanese diet was associated with significantly lower CRP and IL-6 levels. More frequent bathing was associated with lower IL-6, but not specifically predictive of low CRP. This study has confirmed prior evidence for low inflammatory activity in Japanese adults and its association with several behavioral practices common in Japan.

1. Introduction

Although Japan has experienced some of the same secular trends for increases in type 2 diabetes and cardiovascular disease that have occurred worldwide (Chan et al., 2009; Chen et al., 2013), Japanese adults are still considered to be generally healthy when compared to other countries (Arai et al., 2015). In certain regions, where adherence to traditional diets is higher, such as around Okinawa, many elderly adults have a life expectancy of more than 85 years and a lower propensity for age-related declines in cognitive function (Yamori et al., 2001). Some of these health benefits are likely due to less obesity and public health policies that encourage physical activities, such as walking (Tsuji et al., 2003), as well as early instruction in schools about healthy eating habits (Tanaka & Miyoshi, 2012; Miyoshi et al., 2012) and an effective, universal health care delivery system (Zhang & Oyama, 2016). However, there is also evidence that East Asians, including Japanese, may be less prone to activate inflammatory physiological pathways than are some other racial and ethnic groups. A number of previous studies have demonstrated that basal levels of two prominent inflammatory biomarkers, C-reactive protein (CRP) and interleukin-6 (IL-6), are lower among Japanese than in adults from European and African family backgrounds (Saito et al., 2007; Coe et al., 2011).

It is possible that a number of behavioral and dietary practices in Japan help to modulate inflammatory physiology (Willcox et al., 2014). Tea (*Camellia sinensis*), especially green tea, is commonly consumed; a large survey found that 80% of Japanese drink 1 or more cups of green tea per day (Sasazuki et al., 2004). Further, an epidemiological study of 90,914 Japanese adults between 40 and 69 years of age indicated that more frequent drinking of green tea was associated with less cardiovascular disease and all-cause mortality, including from cancer (Saito et al., 2015). Belief in the health benefits of green tea go back to 12th century when the Japanese Zen priest Eisai brought tea plant seeds from China to grow for medicinal purposes (Fujiki et al., 2002). Many recent studies have documented that constituents in both green and black tea, including free radical and oxygen-scavenging flavonoids and polyphenols, are beneficial for health (Chatterjee et al., 2012; Oh et al., 2013; Senanayake, 2013; Zhao et al., 2019; Cabrera et al., 2006). In

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some cases, the antioxidant, antibacterial and anti-inflammatory actions appear to be potent enough to exert protective and therapeutic benefits for diseases with inflammatory features, including arthritis, heart disease, and cancer (Saito et al., 2015; Tao and Lambert, 2014). It is also likely that other components of the Japanese diet play a role in reducing inflammatory responses (Kuriyama et al., 2016; Shimazu et al., 2007). While more research has been conducted on the salubrious benefits of the Mediterranean diet (Carluccio et al., 2003), many have suggested there are equivalent, health-promoting aspects of the traditional Japanese diet, which typically includes a lot of seafood (Miyoshi et al., 2012; San Gabriel et al., 2018; Willcox et al., 2014). Fish are known to be high in omega-3 fatty acids, which have anti-inflammatory actions (Calder, 2010; Murakami et al., 2005). Several epidemiological studies have demonstrated that the traditional Japanese diet, which includes seafood and vegetables, is associated with lower disease morbidity and extended longevity (Abe et al., 2020; Kurotani et al., 2016). Our analyses considered the contribution of tea, seafood and vegetable consumption as a composite index of a healthier Japanese diet and separately as individual practices.

Perhaps one custom most uniquely associated with Japanese culture is partaking in relaxing hot baths. Taking baths is common; a survey found that 65% of respondents bath seven or more times a week (Hayasaka et al., 2010). The bathing traditions of *onsen* (hot-spring baths) and *sento* (public bathing) have been cultivated over many centuries. Bathing has been promoted mostly for hygienic and therapeutic reasons, but there are also social and psychological benefits associated with communal bathing. More recently, the importance of public baths has diminished somewhat by the availability of private bathtubs or *ofuro* in Japanese homes, but a belief in the therapeutic benefits of mineral water bathing in *onsen* is still widespread. Japanese are obviously not the only people who value raising body temperature and warmth, such as the common practice in Northern Europe of spending time in saunas or the use of sweat lodges among some Native American groups (Kunutsor et al., 2018; Livingston, 2010; Peräsalo, 1988). A number of investigators have attempted to acquire empirical evidence to show that periodic increases in body temperature can influence our physiology, with effects on cardiometabolic health (Heinonen & Laukkanen, 2018) and cytokine biology (Kiecolt-Glaser et al., 2015; Raison et al., 2018).

One aim of the following analyses was to extend previous findings of low levels of CRP and IL-6 among middle-aged and older Japanese adults. In addition, a more specific goal was to determine if 4 behavioral and dietary practices common in Japan– tea-drinking, frequent seafood and vegetable consumption, and regular bathing— were associated with individual differences in inflammatory physiology in an adult population with generally low blood levels of CRP and IL-6. Finally, because of the known influence of demographic factors and obesity on both CRP and IL-6, the regression models controlled for variation associated with age, gender, educational attainment, marital status, adiposity (BMI), physical activity, as well as several relevant chronic illnesses (e.g., cardiovascular disease and type 2 diabetes). The *a priori* prediction was that more frequent engagement in these 4 behavioral practices would be correlated with lower levels of both CRP and IL-6.

2. Methods

2.1. Participants

The 382 Japanese participants were a subset (37.2%) of a larger number (1027) of randomly selected middle- and older-aged adults recruited in 2008 to represent the 23 residential wards of Tokyo. All respondents in the Midlife in Japan study (MIDJA) completed demographic and psychological questionnaires, and the biomarker subsample provided blood specimens at a medical clinic near the University of Tokyo. Mean age was 55.5 years (+/-14.0 years, 31–80 years of age), and 72% were married. Age, gender composition, marital status, and education attainment did not differ significantly between participants in the biomarker and survey projects. All procedures were approved by the Health Sciences Institutional Review Board at the University of Wisconsin as well as reviewed by a committee at the University of Tokyo.

2.2. Demographic variables

Age, gender, current marital status, and educational attainment were determined for all participants. Educational attainment was measured on an 8-point scale ranging from 1 (8th grade, junior high school graduate) to 8 (graduate school).

2.3. Relevant health measures

To control for health behaviors relevant to inflammation, physical activity (the frequency of having a good fitness workout over the past month was included as a covariate and rated from never [1], to 1–6 times [2], and 7 or more occasions [3]). In addition, smoking status (currently smoking or not) and alcohol consumption (number of drinks consumed per week) were also included as covariates. Two high scores for alcohol consumption were Winsorized to 3 SD from the mean; all scores were then log-transformed to reduce skewness. To control for the influence of relevant illnesses, a number of chronic conditions that could affect inflammatory activity were also considered (e.g., hypertension, heart disease; Friedman & Herd, 2010) along with a measure of obesity (Body Mass Index; BMI, weight/height^2, kg/m^2) and HA1c values above 6.5% as an indicator of type 2 diabetes.

2.4. Life style variables

Respondents rated how often they had engaged in a number of different behavioral activities. To test the predicted hypotheses, their responses to 4 questions were analyzed: 1) Tea consumption: How much do you usually drink green or black tea (assume a cup = 200 mL)? Answers could range from never to 8 or more times a day, and were scored from 1 to 7: (never [1], once/week [2], 1–3 times/week [3], almost daily [4], 1–3 times/day [5], 4–7 times/day [6], 8 or more times/day [7]). 2) Seafood: In an average week how often do you eat fish (e.g., tuna, salmon, mackerel, eel, etc.)? Response options ranged from never [1], about once/week [2], 1–2 times/week [3], 3–4 times/week to [4], to 5 or more times/week [5]. 3) Vegetables: On an average day how many items of vegetables do you eat (including 100% juice). Response options ranged from none [1], less than 1 items/day [2], 1–4 items/day [3], 5–9 items/day to [4], to 10 or more items/day [5]. 4) Bathing. Finally, the frequency of taking a relaxing bath was rated over the past month from never [1], to 1–6 times [2], and 7 or more occasions [3]. Histograms showing the response frequencies across all participants for each behavior are provided in Supplemental Materials (Supplemental Fig. 1).

2.5. Inflammatory measures

Blood was obtained from 214 women and 168 men during visits to a medical clinic near the University of Tokyo. Over 95% were obtained between 0900 and 1145, with most of the remainder by 1330; just 8 in the afternoon by 1530. Serum specimens were frozen in an ultracold freezer and shipped on dry ice by overnight courier for analysis in the United States. Serum IL-6 levels were determined by high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine, R&D Systems, Minneapolis, MN), with a lower sensitivity of detection at 0.16 pg/mL. All values were quantified in duplicate; any value over 10 pg/mL was re-run in diluted sera to fall on the standard curve. The intra-assay coefficient of variance (CV) was 4.1% and the inter-assay CV was 12.9% (generated by inclusion of a low and high IL-6 serum pool in each assay). Although the inter-assay CV may seem high, it reflects the many values at low concentrations down below or at 1 pg/mL, where a small shift from 0.87-to-1.13 pg/mL if re-run would still be readily distinguished from a higher IL-6 value at 3.0 pg/mL (2.61-to-3.39 pg/mL). In addition, all samples were allocated randomly to the 10 kits, which were run proximally after all samples were collected; there was no evidence for systematic upward or downward drift across assays. High sensitivity CRP was assessed with a particle- enhanced immunonepholometric assay (Tracy Laboratory, University of Vermont). Briefly, polystyrene particles were coated with monoclonal antibodies to CRP, which in the presence of CRP results in an antigen agglutinate and increased light intensity that can be measured on a BNII nephelometer (Seimans Healthcare Diagnostics, Deerfield, IL). The assay range was 0.16–1100; the intra-assay CV is 2.3–4.4%, and the inter-assay CV ranged from 2.1 to 5.7%. Eight high IL-6 and CRP values were Winsorized to 3 SD from the mean and log-transformed to address skewness and lessen a possible influence of outliers on the statistical results.

Glycosylated hemoglobin (HA1c) was determined from fresh whole blood on the day of collection at a clinical laboratory (Syowa Medical Science, Tokyo). After calibrating the HA1c values to typical scales in the US, a cutoff of 6.5% was used to identify individuals meeting established criterion for poorer glucoregulation and Type 2 diabetes. The reference calibration curve was standardized across both countries by testing 10 blood samples both in Tokyo and after overnight courier delivery to a clinical laboratory in the US (Unity Point Health Meriter, Madison, WI).

2.6. Statistical analyses

Descriptive statistics were generated for all variables. A composite indicator of the Japanese Diet was generated by standardizing the frequency of tea drinking, fish and vegetable consumption, and averaging the standardized scores for each participant. In addition to considering the composite Japanese Diet score, dietary factors were each tested separately in follow-up analyses. To test the association between life style variables (Japanese Diet and/or Bathing) and inflammatory activity, a series of hierarchical multiple regression analyses were run using each life style variable as a predictor and each inflammatory measure as the outcome in separate analyses. Demographic variables were entered in Model 1 and then a life style variable added in Model 2. Lastly, relevant behaviors and health conditions, including HA1c above 6.5%, were added in Model 3 to determine whether the associations remained significant after controlling for potentially confounding influences. Alpha was set at p less than 0.05. Because 8 high IL-6 and CRP values (2% of the 382 values) were set at the 3 SD point, all models were also rerun a second time with these participants omitted. The significance of the main findings did not change. Therefore, all participants were retained because the study aim was to consider the continuum from healthy to unhealthy, and for the conclusions to be representative of Tokyo residents.

3. Results

3.1. Descriptive analyses

Descriptive statistics for all demographic and predictor variables and the two inflammatory outcome measures are presented in Table 1. Histograms illustrating the distribution of scores for the 4 life variables are shown in Supplemental Fig. 1. The scores indicate there was sufficient variation in tea drinking, seafood and vegetable consumption, and bathing frequency to compare differences across participants. This descriptive summary also indicates that middle-aged and even older Japanese adults have relatively low levels of both IL-6 and CRP, but there was still the expected increase in the circulating levels of both proteins with age, and males had higher levels than females (shown in Supplemental Fig. 2).

Table 1
Descriptive statistics for demographic predictor and outcome variables.

	M (*SD*) or %	range
Demographic variables		
Gender (% female)	56%	
Age	55.47 (14.04)	31–80
Educational attainment	4.65 (2.03)	1–8
Currently married (% yes)	71.9%	
Lifestyle variables		
Drinking tea	3.94 (1.39)	1–7
Eating seafood	3.36 (0.90)	1–5
Eating vegetables	3.45 (0.72)	1–5
Taking a bath	2.29 (0.71)	1–3
Inflammatory measures		
IL-6 (pg/mL)	1.64 (2.11)	0.03–21.20
Winsorized IL-6 (pg/mL)*	1.55 (1.56)	0.03–7.97
CRP (ug/mL)	0.76 (2.00)	0.15–30.70
Winsorized CRP (ug/mL)*	0.67 (1.17)	0.15–6.75
Health behavior		
Physical exercise	1.91 (0.71)	1–3
Current smoker (% yes)	21.5%	
Alcohol (drinks/week)	7.24 (11.75)	0–140.0
Winsorized Alcohol consumption	6.96 (9.66)	0–42.49
Health conditions		
Body Mass Index	22.58 (2.96)	15.85–33.35
HA1c (% over 6.5%)	10.2%	
Chronic conditions	0.52 (0.78)	0–4

Note. IL-6 = Interleukin-6; CRP = C-reactive protein.
* 8 high values for IL-6 and CRP were Winsorized to 3 SD from the mean. To reduce skewness, 2 scores for very frequent drinking were also set at the 3 SD point. All values were log-transformed before the statistical analyses.

3.2. Influence of life style variables on inflammatory physiology

Statistical results from the modeling of IL-6 are presented in Table 2. In Model 1, males had higher levels of IL-6 than females, and older adults had higher levels of IL-6 than younger Japanese. In Model 2, supporting the primary hypothesis, more frequent consumption of the Japanese Diet, β = -0.10, SE_β = 0.03, $t(350)$ = 3.65, p < .001, 95% CI [-0.15, -0.04], R^2 = 0.029, and regularly taking a relaxing bath, β = -0.07, SE_β = 0.03, $t(349)$ = 2.58, p = .010, 95% CI [-0.12, -0.02], R^2 = 0.015, were significantly associated with lower levels of IL-6. Importantly, these relationships remained significant even after controlling for other relevant health behaviors, including physical activity, and illness conditions in Model 3 (Fig. 1A and C). The specific statistical results were: consuming Japanese Diet, β = -0.09, SE_β = 0.03, $t(344)$ = 3.51, p = .001, 95% CI [-0.14, -0.040], R^2 = 0.026 and taking a relaxing bath, β = -0.06, SE_β = 0.03, $t(343)$ = 2.31, p = .022, 95% CI [-0.11, -0.01], R^2 = 0.011.

The results from the statistical models predicting CRP are presented in Table 3. In Model 1, males had higher levels of CRP than females, and older adults had higher CRP than younger Japanese. In Model 2, in keeping with the primary hypothesis, more frequent consumption of the Japanese Diet was associated with lower CRP levels, β = -0.09, SE_β = 0.03, $t(350)$ = 2.88, p = .004, 95% CI [-0.16, -0.03], R^2 = 0.020 (Fig. 1B). However, taking a relaxing bath more regularly was not significantly associated with lower CRP, β = 0.02, SE_β = 0.03, $t(349)$ = 0.53, p = .595, 95% CI [-0.05, 0.08], R^2 = 0.001 (Fig. 1D). Importantly, the significant association between CRP and consuming the Japanese Diet remained even after controlling for relevant health behaviors, including physical activity and illness conditions in Model 3; β = -0.08, SE_β = 0.03, $t(344)$ = 2.47, p = .014, 95% CI [-0.14, -0.02], R^2 = 0.014.

Additional analyses were conducted to test each of the diet variables separately. When each of the diet variables was entered separately into

Table 2
Regression coefficients from models predicting IL-6 levels based on the Japanese diet score and frequency of taking a relaxing bath.

	Model 1 (demographics)		Model 2 (lifestyle)		Model 3 (health covariates)	
	β (*SE*)	*t*	*β* (*SE*)	*t*	*β* (*SE*)	*t*
	Japanese diet (drinking tea, eating fish, and eating vegetables)					
Gender	-0.134 (0.036)	3.73**	-0.113 (0.036)	3.16**	-0.033 (0.042)	0.79
Age	0.010 (0.001)	7.78***	0.011 (0.001)	8.52***	0.010 (0.001)	7.26***
Education	-0.013 (0.009)	1.47	-0.009 (0.009)	1.02	-0.008 (0.009)	0.85
Married	0.011 (0.039)	0.27	0.021 (0.039)	0.54	0.004 (0.038)	0.10
Japanese diet			-0.096 (0.026)	3.65***	-0.092 (0.026)	3.51**
Exercise					-0.042 (0.024)	1.75
Smoking					0.016 (0.044)	0.36
Drinking					0.052 (0.033)	1.56
BMI					0.018 (0.006)	2.77**
HA1c					0.112 (0.059)	1.90
Chronic conditions					0.015 (0.024)	0.61
ΔR^2	0.212		0.029		0.042	
	Taking a bath					
Gender	-0.131 (0.036)	3.63***	-0.121 (0.036)	3.36**	-0.040 (0.043)	0.94
Age	0.010 (0.001)	7.75***	0.011 (0.001)	8.20***	0.010 (0.001)	6.94***
Education	-0.014 (0.009)	1.49	-0.015 (0.009)	1.65	-0.013 (0.009)	1.43
Married	0.006 (0.039)	0.16	0.011 (0.039)	0.27	-0.006 (0.039)	0.15
Bath			-0.065 (0.025)	2.58*	-0.060 (0.026)	2.31*
Exercise					-0.031 (0.025)	1.20
Smoking					0.035 (0.044)	0.79
Drinking					0.047 (0.034)	1.39
BMI					0.017 (0.006)	2.56*
HA1c					0.131 (0.059)	2.21*
Chronic conditions					0.012 (0.025)	0.47
ΔR^2	0.212		0.015		0.042	

Note. Eight high values for IL-6, as well as high outliers for frequent alcohol consumption were Winsorized to 3 SD from the mean. All values were then log-transformed. * $p < .05$, ** $p < .01$, *** $p < .001$.

the models to predict IL6 (Supplemental Table 4), all three variables significantly predicted IL-6, even in the full model (Model 3): drinking tea, β = -0.03, SE_β = 0.01, $t(335)$ = 2.23, p = .027, 95% CI [-0.05, -0.003], R^2 = 0.011, eating fish, β = -0.05, SE_β = 0.02, $t(344)$ = 2.37, p = .018, 95% CI [-0.09, -0.01], R^2 = 0.012, and eating vegetables, β = -0.05, SE_β = 0.02, $t(342)$ = 2.23, p = .026, 95% CI [-0.10, -0.01], R^2 = 0.011 (see Supplemental Fig. 3). For the analyses of CRP (Supplemental Table 5), none of the individual diet items significantly predicted CRP levels on their own in the full model after controlling for levels of physical activity (Model 3); drinking tea, β = -0.03, SE_β = 0.02, $t(335)$ = 1.87, p = .063, 95% CI [-0.06, 0.002], R^2 = 0.008, eating fish, β = -0.04, SE_β = 0.02, $t(344)$ = 1.80, p = .072, 95% CI [-0.09, 0.004], R^2 = 0.007 (see Supplemental Fig. 3). However, prior to allocating variance attributable to physical activity, endorsement of more frequent tea drinking was significantly associated with lower CRP levels. Physical activity and tea drinking were not directly correlated in pairwise testing (r = 0.00, p = .97), nor did level of physical activity directly affect CRP levels, but its inclusion in the models lessened the predictive significance of tea drinking. Finally, it should be emphasized that CRP for most participants was lower than typical clinical cutoffs for considering CRP to be elevated in adults from other countries (that is, most values were below 3 µg/mL).

4. Discussion

This analysis has confirmed previous findings of relatively low levels of CRP and IL-6 in Japanese adults, and now extends those conclusions to show that the low inflammatory activity may be associated with dietary preferences and behavior common in Japan (Shimazu et al., 2007; Kuriyama et al., 2016). However, it should still be acknowledged that there are also likely to be some heritable factors underlying the lower levels of these two pro-inflammatory proteins because single nucleotide polymorphisms (SNP) and gene promoters associated with inflammatory physiology, including ones that govern the magnitude of IL-6 responses to disease, vary in frequency distributions across racial groups and countries (Chen et al., 2012; Galicia et al., 2006; Okada et al., 2011; Tanaka et al., 2005; Yamada et al., 2003; Yeh et al., 2010). Further, both CRP and IL-6 have been shown repeatedly to be associated with adiposity, and most Japanese do not evince the more extreme obesity that has become prevalent in other countries. It should be highlighted that the mean BMI for all participants in the current study was only 22.6, which would be considered thin in a survey of American or European populations. A number of prior papers have already documented that a pivotal indicator of obesity among East Asian adults is crossing a BMI threshold of 25, which is associated with an increased risk for cardiovascular disease and type 2 diabetes (Chen et al, 2013; Rush et al., 2009). Beyond the effects of adiposity and heritable factors, however, it appears that some behavioral and life style practices contribute to the maintenance of low circulating levels of CRP and IL-6.

Specifically, our analyses suggest the importance of diet, including the consumption of fish and vegetables, and more frequent drinking of tea. Many *in vitro* experiments have demonstrated that marine omega-3 fatty acids and constituents in tea (i.e., flavonoids and polyphenols) can directly exert anti-inflammatory actions (Almajano et al., 2008; Calder, 2010; Kang & Weylandt, 2008; Zhao et al., 2019). In addition, other ingredients in some regional Japanese cuisines, including the phytonutrients in the purple sweet potato consumed by many in Okinawa have significant anti-inflammatory properties, derived from the phenolic acids, flavonols, anthocyanins and carotenoids in plant-based foods (Willcox et al., 2014). Endorsement of more frequently engaging in these dietary practices could also reflect adherence to a traditional life style and a greater personal awareness of the importance of health-promoting behavior. For example, it was of interest that among the demographic variables, age was significantly associated with more frequent fish consumption (r = 0.24, p < .001), being more common in older Japanese adults. While the magnitude of the associations in the statistical models would be considered to be in the small-to-moderate range by Cohen's criteria, the evidence for an effect of diet and tea drinking was obtained after considering the influence of many other

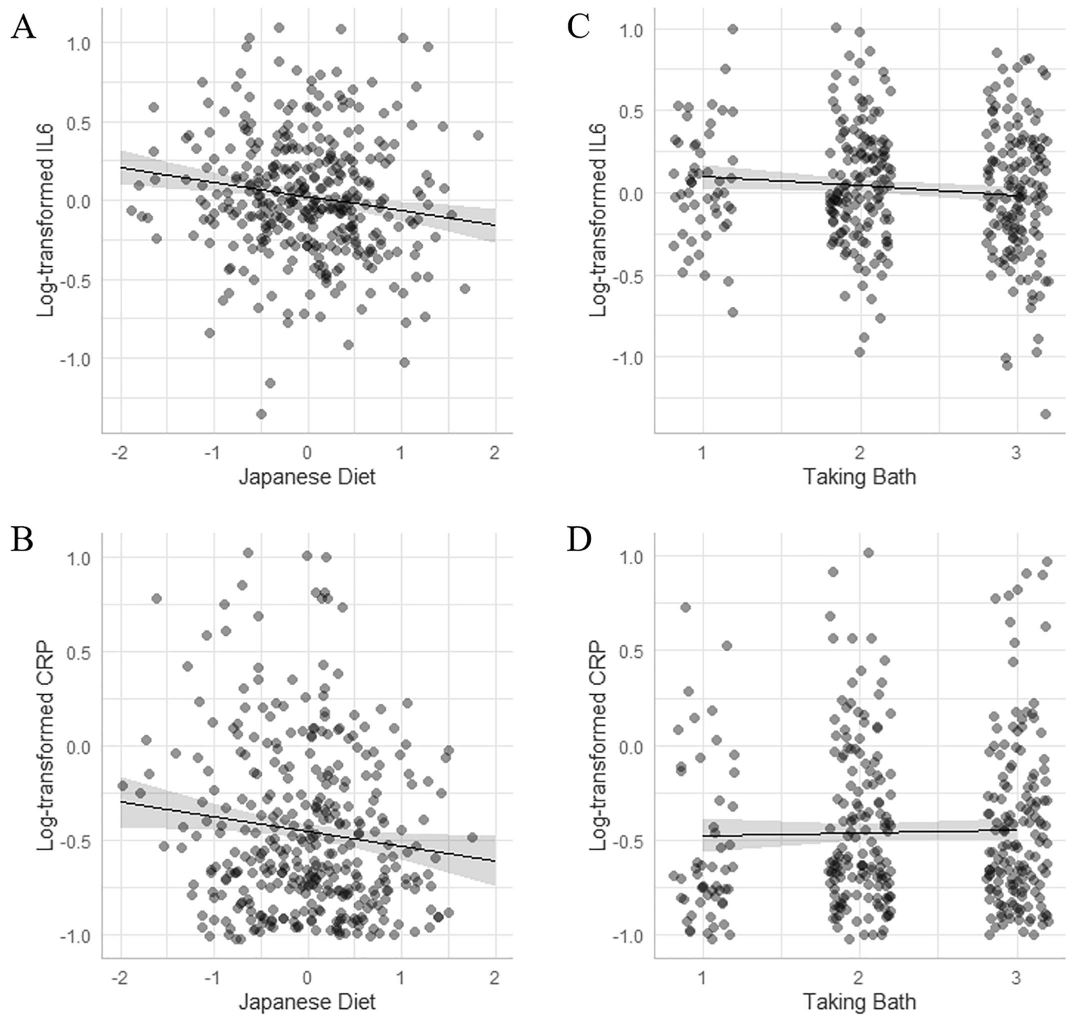

Fig. 1. IL6 levels as a function of consuming a more traditional Japanese diet (A) and taking a bath more regularly (C). CRP levels as a function of consuming a Japanese Diet (B) and more frequently taking a relaxing bath (D). There was a significant association between both predictors and IL-6, as well as for consuming a Japanese Diet and CRP. Scatter plots show raw data; regression lines and confidence bands (95%) take covariates into consideration. Eight IL-6 and CRP were Winsorized to 3 SD from the mean; then all values were log transformed.

variables, including age, adiposity, physical activity and poor glucoregulation as indexed by higher HA1c values.

There are likely to be some other aspects of the traditional diet, even at the level of digestive processes among East Asians, that should be considered (Kuriyama et al., 2016; Kuroda et al., 2011; Yoshiike et al., 2007). For example, it has been shown that East Asians are typically able to extract more of the anti-inflammatory and health-promoting benefits from eating soy products (Dijsselbloem et al, 2004). Nearly twice as many are equol producers (50–60%) when compared to Europeans (25–30%), reflecting differences in their gut microbiota and then the downstream synthesis of phytoestrogens (Adlercreutz et al., 1991; Akaza et al., 2004; Miyanaga et al., 2003; Song et al., 2006). Isoflavones (including two phytoestrogens, genistein and daidzein) are thought to compete with endogenous estradiol for estrogen receptors, which could influence inflammatory physiology (Nigata et al., 1998). In contrast, if Asians consume a westernized diet, which is more common among Asians living in the US or Brazil, then there is a significantly increased risk for both cardiovascular disease and type 2 diabetes (Marmot et al., 1975; Ueshima et al., 2003; Moriguchi et al., 2004). In fact, the risk from eating high fat foods can become greater than for adults from European family backgrounds who consume a similar diet.

While the levels of CRP and IL-6 were low in our study, it should be noted that both of these inflammatory proteins can and do rise with age and with clinical illness among Japanese adults. Many clinical studies in Japan, China and Taiwan have shown that an increase in CRP and IL-6 levels is a sensitive predictor of poor health as it is in American and European patients (Saito et al., 2007; Ye et al., 2007). In fact, in our data, older age was significantly associated with higher levels of CRP and IL-6. But the values may still remain low relative to what is observed in many elderly American and European patients. We also found that both CRP and IL-6 were associated with HA1c values, which differs from one prior report that found the increments were small to nonexistent in Japanese patients with type 2 diabetes (Taniguchi et al., 2006). The low levels of CRP and IL-6 typically found in healthy Japanese adults may also help to explain why several studies of Japanese and other East Asian populations had more difficulty linking up inflammatory measures with stress and negative emotions than when conducting similar analyses of Americans descended from European family backgrounds (Curhan et al., 2014; Miyamoto et al., 2013; Kitayama et al., 2015; Martikainen et al., 2001). Further, even studies that focused specifically on the neural and cognitive changes associated with Alzheimer's among the extremely old in Japan failed to detect large correlations with CRP and IL-6, or discerned only a modest relationship (Katsumata et al., 2012; Silbert et al., 2018). The strong relationship between aging and inflammation, which has been termed *inflamm-aging* (Franceschi et al., 2000) does not appear to be as prominent among older Japanese adults.

Notwithstanding several novel findings from our analyses, some

Table 3
Regression coefficients from models predicting CRP levels based on the Japanese diet scores and frequency of taking a relaxing bath.

	Model 1 (demographics)		Model 2 (lifestyle)		Model 3 (health covariates)	
	β (SE)	*t*	*β (SE)*	*t*	*β (SE)*	*t*
	Japanese diet (drinking tea, eating fish, and eating vegetables)					
Gender	-0.224 (0.044)	5.11***	-0.204 (0.044)	4.64***	-0.107 (0.051)	2.09*
Age	0.006 (0.002)	3.97***	0.007 (0.002)	4.54***	0.007 (0.002)	4.04***
Education	-0.014 (0.011)	1.23	-0.010 (0.011)	0.87	-0.005 (0.011)	0.42
Married	0.068 (0.048)	1.43	0.079 (0.047)	1.66	0.057 (0.047)	1.23
Japanese diet			-0.093 (0.032)	2.88**	-0.078 (0.032)	2.47*
Exercise					-0.002 (0.029)	0.08
Smoking					0.176 (0.053)	3.29***
Drinking					0.003 (0.040)	0.07
BMI					0.023 (0.008)	2.95**
Ha1c					0.098 (0.072)	1.36
Chronic conditions					0.002 (0.030)	0.08
ΔR^2	0.135		0.020		0.061	
	Taking a bath					
Gender	-0.222 (0.044)	5.06***	-0.225 (0.044)	5.08***	-0.123 (0.052)	2.39*
Age	0.006 (0.002)	4.04***	0.006 (0.002)	3.80***	0.006 (0.002)	3.57***
Education	-0.013 (0.011)	1.20	-0.013 (0.011)	1.17	-0.007 (0.011)	0.63
Married	0.072 (0.048)	1.51	0.071 (0.048)	1.49	0.050 (0.047)	1.07
Bath			0.017 (0.031)	0.53	0.016 (0.031)	0.52
Exercise					-0.012 (0.031)	0.39
Smoking					0.193 (0.053)	3.60***
Drinking					-0.001 (0.041)	0.03
BMI					0.022 (0.008)	2.77**
Ha1c					0.114 (0.072)	1.59
Chronic conditions					0.000 (0.030)	0.02
ΔR^2	0.138		0.001		0.067	

Note. Eight high values for CRP and high outlier scores alcohol consumption were Winsorized to 3 SD from the mean. All values were then log transformed. * $p < .05$, ** $p < .01$, *** $p < .001$.

limitations of the study design should be acknowledged. First, the participants were recruited entirely from Tokyo, and there are important regional differences in Japanese cuisine, and variation in general health across cities in Japan (Chan et al., 2009; Decoda Study Group, 2003). However, it should be reiterated that the recruitment process did employ rigorous guidelines, using a professional survey center to ensure that the age and gender composition was representative of all 23 neighborhood wards in Tokyo. It is also important to acknowledge that the behavioral information was acquired from survey questions, and only at one point in time. Thus, the demonstrations of association cannot be used to ascertain causality. Fortunately, there are enough other studies on the benefits of adherence to a traditional Japanese diet, which were conducted prospectively with long-term follow-ups of morbidity and mortality, that it is reasonable to conclude with some confidence that a traditional diet is linked with a lower risk for both cardiovascular disease and type 2 diabetes, both of which are worsened by inflammatory processes (e.g., Abe et al., 2020; Okada et al., 2018). Dietary practices have also been associated with sleep health in Japan; with both poor diet linked to insomnia and a faster initiation of sleep when eating the more traditional diet (Kurotani et al., 2015; Matsuura et al., 2020). Finally, only 4 behavioral practices were considered in this modeling, but they had been selected purposefully to represent personal adherence to more traditional customs and healthier practices. Future research should now interrogate each of the behavioral and dietary variables more specifically, including the influence of meal portion size, the drinking of different kinds of tea, as well the consumption of specific constituents in certain vegetables, types of fish and fermented foods (Masuda et al., 1999; Tang et al., 2015; Tomata et al., 2019).

In addition to specific dietary items, it may also be important to consider the synergistic effects of consuming a combination of foods across the day. Since 2000 the dietary policy recommendations in Japan have been based on a Food Balance Guide, and visualized as a "*spinning top*" (Ministry of Health, Labor and Welfare) to emphasize a "balanced" diet, rather than the food *pyramid* icon used in the United States, which pictures a hierarchy of high priority items. In one 10-year prospective study, adherence to the balanced diet recommended by the Japanese Food Guide Spinning Top was associated with a 15% reduction in total mortality rate among 79,594 Japanese adults between 57 and 75 years of age (Kurotani et al., 2016).

One especially innovative aspect of the current analysis was the inclusion of regularly taking relaxing baths. There has been increasing interest in the benefits of raising body temperature through immersion in hot baths or in saunas as a means to improve cardiovascular and metabolic health. Our data suggest there may also be a tonic regulatory effect on inflammatory activity, at least for IL-6. As mentioned in the Introduction, bathing has been a custom in Japan for many centuries, and the belief in its psychological and medicinal benefits remains widespread. Research conducted in Japan has suggested there may also be other life style practices that can have immunomodulatory effects, such as the benefits of exposure to natural settings and taking relaxing walks in the forest, called forest-bathing or *shinrin-yoku* (Hansen et al., 2017; Li, 2010). But it is especially appropriate to now link up the Japanese practice of hot baths with lower IL-6 levels, given the seminal role played by Dr. Kishimoto and colleagues (Akira et al., 1993; Kishimoto, 2005; Tanaka et al., 2014) in demonstrating the importance of this inflammatory cytokine for health and disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.08.008.

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