

Research Article

Association between Lifestyle Habits Questionnaire and Plasma Free Amino Acid Profile in Japanese Rural Community Dwellers

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Abstract

The plasma free amino acid (PFAA) profiles are demonstrated to be altered by overnutrition and subsequent insulin resistance, and/or protein malnutrition in generally healthy subjects. Although, the measurement of PFAAs to evaluate the risk of overnutrition and protein malnutrition is potentially useful, large scale social implementation present several difficulties. Currently, rigorous measurement of PFAAs using high-performance liquid chromatography–electrospray ionization mass spectrometry, following the collection of fasting blood in the morning in hospitals with strict sample management, is required, which can be a burden for local hospitals. In this study, we designed a simple lifestyle habits questionnaire consisting of 19 questions reported to be associated with overnutrition and protein malnutrition, suitable for Japanese rural communities. And then, we investigated the association between PFAAs and the results of the questionnaire in 1,764 Japanese local community dwellers. The results of questions regarding lifestyles leading to overnutrition and subsequent body weight gain were associated with higher concentrations of most essential amino acids including branched chain amino acids and aromatic amino acids. On the other hand, results of questions related to lifestyles leading to protein malnutrition were associated with lower concentrations of some essential amino acids. The results of questions regarding sleep duration, frequency of dairy food intake, snack habit, gait speed, fruit and vegetable intake had little impact on PFAA profiles. This simple lifestyle habits questionnaire could be a potential screening tool to predict alterations of PFAA profiles. Further validations of the associations with other populations are necessary before large scale social implementation.

ABBREVIATIONS

PFAAs: Plasma Free Amino Acids; BCAAs: Branched-Chain Amino Acids; AAAs: Aromatic Amino Acids; Ala: Alanine; Arg: Arginine; Asn: Asparagine; Cit: Citrulline; Glu: Glutamate; Gln: Glutamine; Gly: Glycine; His: Histidine; Ile: Isoleucine; Leu: Leucine; Lys: Lysine; Met: Methionine; Orn: Ornithine; Phe: Phenylalanine; Pro: Proline; Ser: Serine; Thr: Threonine; Trp: Tryptophan; Tyr: Tyrosine; Val: Valine; α ABA: α -Amino Butyric Acid; SE: Standard Error; SPRC: Standardized Partial Regression Coefficients; 2Na·EDTA: Disodium Ethylenediaminetetraacetate

INTRODUCTION

Recently, accumulating evidence has revealed that the concentrations of plasma free amino acids (PFAAs) are potential biomarkers for overnutrition and subsequent insulin resistance

[1-3], and/or protein malnutrition [4-6]. Among the PFAAs, especially branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs), are associated with visceral obesity, insulin resistance, and diabetes mellitus in several cross-sectional and prospective cohort studies [1,7-10]. BCAA concentrations are elevated in obese humans and animal models [9,11,12]. This elevation is caused by insulin resistance which decreases utilization of amino acids and uptake of BCAAs into muscles [13,14]. Furthermore, insulin resistance decreases expression of adipose-tissue BCAA catabolizing enzymes, leading to decreased BCAA metabolism in visceral adipose tissue [13,15,16]. Other plasma free amino acid concentrations are also altered in people with high visceral obesity [7]; alanine (Ala), glutamate (Glu), phenylalanine (Phe), proline (Pro), tryptophan (Trp) and tyrosine (Tyr) are elevated, while glycine (Gly) and serine (Ser) are decreased. It is believed that this alteration is caused by a

combination of insulin resistance-induced accelerated protein break down in muscle and changes in the gluconeogenesis set point in liver.

On the other hand, insufficient protein intake could trigger low concentrations of essential and semi-essential amino acids in blood [4,5]. Insufficient protein intake, which is called protein malnutrition, is common across varying populations, particularly in elderly subjects. It has been associated with increased risk of sarcopenia, heart failure, impaired immune response, impaired respiratory function, delayed wound healing, overall increased complications and increased mortality in various populations [17-19]. Especially, the importance of ingesting enough amount of protein is demonstrated in the elderly population [20]. Furthermore, in generally healthy population who go to annual health checkup, low essential and semi-essential amino acid concentrations in blood was significantly associated with the protein malnutrition-associated markers, anemia-associated markers, sympathetic nerve activity-associated markers, and inflammation and immune function-associated markers [6,21].

Although, the measurement of PFAAs to evaluate the risk of overnutrition and protein malnutrition is potentially useful, social implementation involves several difficulties. The fasting blood has to be collected in the morning in hospitals with strict sample management to keep metabolites stable, and the blood has to be transported to the site where centrifugation can be done for plasma preparation. The rigorous measurement of PFAAs requires high-performance liquid chromatography-electrospray ionization mass spectrometry followed by pre-column derivatization [21-26]. Thus, we hypothesized that if the results of a simple questionnaire for lifestyle habits could be correlated to PFAA concentrations, then this could be used as an initial screening tool for PFAA alterations.

In this study, we designed a lifestyle habits questionnaire associated with overnutrition and protein malnutrition, suitable for Japanese rural community dwellers. And then, we quantified PFAA concentrations and investigated the association with the results of lifestyle habits questionnaire in 1,764 participants.

MATERIALS AND METHODS

Participants

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Saihaku Hospital (Tottori, Japan). A total of 2,809 Japanese participants who visited Saihaku Hospital from January 2012 to June 2014 were enrolled. All participants were generally healthy and at least 20 years of age (mean age: 62.9 ± 11.1 years) (Table 1). Exclusion criteria included pregnancy, severe mental disorders, and cancer.

The lifestyle habits questionnaire

The lifestyle habits questionnaire with 19 items was used to assess the dietary habits, alcohol consumption, sleeping habits, physical activity and body weight change (Table 2) [27-37], which was optimized for the lifestyle of Japanese rural community dwellers. Q.1, Q.2, Q.3, Q.4, Q.5, Q.6, and Q.7 are related with overnutrition lifestyle habits, while Q.15, Q.16, Q.17, Q.18 and Q.19 are related with protein malnutrition lifestyle. Q. 8, Q. 9, Q.

10, Q. 11, Q. 12, Q. 13 and Q. 14 are related with sleep duration, frequency to intake dairy food, snack habit, gait speed, fruit and vegetable intake. The questionnaire survey was conducted via mail from August 2014 to September 2014. The participants answered using two scales (Yes/No) to the each question. Finally, 1,764 participants (62.8% response rate) delivered a completed questionnaire.

Measurement of plasma free amino acid concentrations

At Saihaku Hospital, blood samples (5 mL) were collected from forearm veins after overnight fasting into tubes containing disodium ethylenediaminetetraacetate (2Na-EDTA) that were immediately placed on ice. Plasma was prepared by centrifugation at 3,000 rpm at 4 for 15min. The plasma amino acid concentrations were measured by high-performance liquid chromatography-electrospray ionization mass spectrometry followed by precolumn derivatization as previously described [22-26]. The following 21 amino acids were measured: Ala, arginine (Arg), asparagine (Asn), citrulline (Cit), Glu, glutamine (Gln), Gly, histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met), ornithine (Orn), Phe, Pro, Ser, threonine (Thr), tryptophan (Trp), Tyr, valine (Val), and α -Amino butyric acid (α ABA).

Statistical analyses

The statistical analyses except for the estimation of linear regression models were performed using the JMP 13.2.1 program (SAS Institute Inc., Cary, NC, USA). Welch's t-tests were used to compare male and female. Categorical data were analyzed using chi-square test. The data in the tables are expressed as the mean \pm SE.

Relationship between plasma free amino acid concentrations and answer of each question (Yes = 1, No = 0) was evaluated in terms of sex-adjusted standardized partial regression coefficients. The R language (R version 3.2.4 Revised, <http://www.r-project.org/>) was implemented for the estimation of linear regression models. Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

We generated the lifestyle habits questionnaire which is suitable for Japanese rural community dwellers to evaluate the overnutrition and protein malnutrition. This study demonstrated the questions regarding overnutrition and protein malnutrition had association with some of PFAA profiles in 1,764 Japanese participants, and thus, it could be a potential screening tool to evaluate the PFAA profiles.

Table (1) represents the demographics and plasma free amino acid profiles of the participants. The plasma amino acid concentrations were significantly higher in male than in female, except for Gly and Ser, and these concentrations were within the reference intervals for plasma amino acid concentrations in generally healthy Japanese subjects [21]. Table (2) shows the lifestyle habits questionnaire, and Table (3) indicates the number and percent of participants who responded "Yes" to each question. The ratio of the participants who responded "Yes" to Q.1, Q.5, Q.9, Q.12, Q.13 and Q.18 were significantly higher in male than female, while Q.7 and Q.10 were significantly lower in male.

Table 1: Demographic and plasma free amino acid concentrations.

	Male	Female	P
N	755	1009	
Age (y)	66.0 ± 0.4	64.6 ± 0.3	
Amino acids (μmol/L)			
αABA	20.1 ± 0.2	18.4 ± 0.2	***
Ala	361.6 ± 2.8	308.8 ± 2.2	***
Arg	101.2 ± 0.6	92.8 ± 0.5	***
Asn	47.2 ± 0.2	42.9 ± 0.2	***
Cit	33.7 ± 0.3	31.3 ± 0.2	***
Gln	602.4 ± 2.7	585.8 ± 2.0	***
Glu	32.0 ± 0.5	23.7 ± 0.3	***
Gly	208.1 ± 1.6	237.0 ± 2.2	***
His	80.8 ± 0.3	76.0 ± 0.3	***
Ile	66.0 ± 0.5	50.3 ± 0.3	***
Leu	128.5 ± 0.7	102.8 ± 0.5	***
Lys	202.5 ± 1.1	183.9 ± 0.8	***
Met	27.2 ± 0.2	22.6 ± 0.1	***
Orn	53.7 ± 0.5	48.5 ± 0.4	***
Phe	60.4 ± 0.3	53.4 ± 0.2	***
Pro	149.0 ± 1.5	117.4 ± 1.1	***
Ser	107.6 ± 0.6	111.0 ± 0.7	***
Thr	130.3 ± 1.0	115.6 ± 0.8	***
Trp	57.1 ± 0.3	49.5 ± 0.2	***
Tyr	66.5 ± 0.4	57.9 ± 0.3	***
Val	230.6 ± 1.3	195.3 ± 1.0	***

The continuous variables are summarized as means ± standard error (SE). Significant differences between male and female are shown as *P<0.05, **P<0.01, ***P<0.001 according to Welch's t-test.

Table 2: Lifestyle habits questionnaire.

Q.1	I have gained more than 10 kg of body weight compared with 20 years ago (or when I was 18 years old).
Q.2	I usually eat fast and do not stop eating until I become full.
Q.3	I eat most of the meal at dinner or have a habit of eating a midnight snack.
Q.4	I try to limit the amount to eat.
Q.5	I often eat fatty meat such as bacon and sausage.
Q.6	I often eat meals less than 2 times a day.
Q.7	I tend to sit down rather than get up and work during free time, or I do not like exercise.
Q.8	I sleep for less than 5 hours a day.
Q.9	I eat dairy food and drink milk less than 3 times a week.
Q.10	I have a habit of eating snacks.
Q.11	I walk slower compared with others who are in the same sex and the same generations.
Q.12	I rarely eat fruits
Q.13	I eat vegetables less than 350g or 5 dishes a day. *1 dish corresponds a small bowl or a side dish.
Q.14	As a staple food, I eat refined grains such as white rice or white bread rather than unrefined brown rice. (Refined grains include white rice, white bread, udon, and ramen noodle, while unrefined grains include brown rice, rye, millet bread, and buckwheat noodles.)
Q.15	On average, I eat meats less than 1 time a day.
Q.16	On average, I eat seafood less than 1 time a day.

Q.17	Unintentionally, I lost my body weight more than 5% (2.5kg for the 50 kg body weight) during this 3 months.
Q.18	I have a habit of drinking 2 cups of Japanese Sake (or 2 bottles of 500 mL beer) everyday. Half of these criteria for women.
Q.19	I do not have appetite.
All the questions must be answered "Yes" or "No". Original questionnaire is written in Japanese.	

Figure (1) shows the sex-adjusted standardized partial regression coefficients of PFAA against each question and Table (4) shows P-values. The participants who responded "Yes" to the questions of Q.1, Q.2, Q.3, Q.4, Q.5, Q.6, and Q.7 had higher concentrations of most amino acids. These questions are related with overnutrition lifestyle habits. On the other hand, the participants who responded "Yes" to the questions of Q.15, Q.16, Q.17, Q.18 and Q.19 had lower concentrations of some of essential amino acids. These questions are related with protein malnutrition lifestyle. Q. 8, Q. 9, Q. 10, Q. 11, Q. 12, Q. 13 and Q. 14 which are related with sleep duration, frequency to intake dairy food, snack habit, gait speed, fruit and vegetable intake had little impact to PFAA profiles.

Especially, the participants who responded "Yes" to the questions of Q1, Q2, Q3, Q4, and Q5 had significantly higher concentration of most amino acids including BCAAs and AAAs (Figure 1, Table 4), which are consistent with previous cross-sectional and prospective cohort studies [1,7-10]. The PFAA alterations observed in these questions might have been caused by both metabolic changes due to overweight and elevation of dietary intake itself. Studies so far have suggested that metabolic shifts, rather than dietary habits, play a more significant role in PFAA alterations. Tai et al. [38], previously examined PFAA profiles in association with insulin resistance and diet in 263 non-obese Chinese and Asian-Indian men and demonstrated that although dietary protein intake markedly differed between ethnic groups, it did not elevate PFAA concentrations. Rather, PFAA concentrations were strongly associated with HOMA-IR values. It can be considered that combination of insulin resistance-induced accelerated protein break down in muscle and changes in amino acid metabolism in muscle and adipose tissue elevated the amino acid concentrations in these participants [13-16].

The Q.15, Q.16, Q.17, Q.18 and Q.19 are the questions intending to ask protein malnutrition lifestyles and subsequent body weight loss. The participants who answered "Yes" to the questions of Q.15, Q.16, Q.17, Q.18 and Q.19 had significantly lower concentration of some amino acids including BCAAs (Figure 1, Table 4), but much less pronounced compared with associations in Q1 through Q5 asking overnutrition lifestyles. Although, it is well known that insufficient protein intake [4,5], frailty [39], or sarcopenia [40] could trigger low concentrations of some essential and semi-essential amino acids in blood, precise mechanism how each amino acid concentration becomes low has not been well investigated. Compared with the PFAA alterations observed in overnutrition lifestyles, dietary habits rather than metabolic shifts play a more significant role in PFAA alterations in protein malnutrition lifestyles. Among Q.15 through Q.19, Q.19 which asks loss of appetite strongly affected PFAA profiles.

Table 3: The percent of subjects who answered “Yes” to the lifestyle questionnaire.

	All N (%)	Male N (%)	Female N (%)	P		All N (%)	Male N (%)	Female N (%)	P
Q.1	551 (31.5%)	297 (39.7%)	254 (25.3%)	***	Q.11	486 (27.7%)	215 (28.6%)	271 (27.0%)	
Q.2	482 (27.6%)	209 (27.8%)	273 (27.4%)		Q.12	626 (35.8%)	326 (43.6%)	300 (29.9%)	***
Q.3	211 (12.1%)	81 (10.9%)	130 (13.1%)		Q.13	1057 (60.5%)	486 (65.1%)	571 (57.2%)	***
Q.4	539 (30.7%)	218 (29.1%)	321 (32.0%)		Q.14	1516 (86.5%)	648 (86.4%)	868 (86.6%)	
Q.5	311 (17.8%)	170 (22.6%)	141 (14.1%)	***	Q.15	1188 (68.1%)	525 (69.8%)	663 (66.8%)	
Q.6	127 (7.2%)	63 (8.4%)	64 (6.4%)		Q.16	884 (50.6%)	372 (49.5%)	512 (51.5%)	
Q.7	671 (38.4%)	263 (35.0%)	408 (41.0%)	*	Q.17	119 (6.8%)	49 (6.5%)	70 (7.0%)	
Q.8	232 (13.2%)	93 (12.4%)	139 (13.9%)		Q.18	234 (13.5%)	187 (25.3%)	47 (4.7%)	***
Q.9	502 (28.6%)	275 (36.5%)	227 (22.7%)	***	Q.19	62 (3.5%)	19 (2.5%)	43 (4.3%)	0.0503
Q.10	924 (52.8%)	304 (40.4%)	620 (62.1%)	***					

The categorical variables are shown as frequencies and proportions. Significant differences between male and female are shown as *P<0.05, **P<0.01, ***P<0.001 according to chi-square test.

Table 4: Sex-adjusted P-values of standardized partial regression coefficients between each PFAA concentration and the lifestyle-related question.

	Val	Ile	Leu	Phe	Trp	Tyr	His	αABA	Glu	Ala	Met	Thr	Pro	Lys	Arg	Ser	Asn	Gln	Orn	Gly	Cit
Q.1	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.246	0.826	0.172	0.96	0.023	0.001	<0.001
Q.2	<0.001	<0.001	<0.001	0.018	<0.001	0.007	0.004	0.068	<0.001	<0.001	0.001	<0.001	0.001	0.002	0.925	0.492	0.518	0.717	0.943	0.312	0.027
Q.3	0.029	0.03	0.084	0.089	0.001	0.003	0.27	0.479	0.04	0.007	<0.001	0.008	0.01	0.76	0.612	0.019	0.254	0.819	0.124	0.995	0.214
Q.4	<0.001	<0.001	<0.001	0.009	0.018	0.003	0.26	0.003	<0.001	0.302	0.069	0.016	0.018	0.008	0.598	0.142	0.685	0.638	0.136	0.106	0.928
Q.5	0.061	0.019	0.045	0.769	0.014	0.32	0.353	0.647	0.043	0.006	0.043	0.002	0.141	0.04	0.517	0.002	0.749	0.336	0.156	0.195	0.779
Q.6	0.599	0.279	0.938	0.672	0.016	0.804	0.799	0.015	0.319	0.1	0.472	<0.001	0.194	0.481	0.76	0.001	0.463	0.059	0.74	0.139	0.031
Q.7	0.143	0.01	0.34	0.774	0.432	0.03	0.39	0.484	<0.001	0.023	0.077	0.005	<0.001	0.845	0.59	0.36	0.123	0.329	0.226	0.057	0.168
Q.8	0.503	0.575	0.235	0.604	0.27	0.836	0.413	0.949	0.142	0.052	0.328	0.189	0.536	0.988	0.94	0.285	0.779	0.303	0.511	0.675	0.975
Q.9	0.422	0.914	0.557	0.294	0.763	0.079	0.469	0.008	0.95	<0.001	0.196	<0.001	<0.001	0.082	0.313	0.224	0.515	0.931	0.287	0.04	0.42
Q.10	0.633	0.32	0.609	0.637	0.08	0.496	0.881	<0.001	0.676	0.326	0.617	0.305	0.364	0.091	0.143	<0.001	0.087	<0.001	0.2	0.01	0.411
Q.11	0.75	0.1	0.924	0.278	0.011	0.077	0.002	0.001	0.043	0.112	0.35	0.26	0.14	0.845	0.946	0.06	<0.001	0.229	<0.001	0.684	0.011
Q.12	0.047	0.319	0.135	0.069	0.887	0.827	0.323	0.091	0.694	0.552	0.31	<0.001	0.3	0.033	0.356	0.138	0.989	0.016	0.782	0.343	0.77
Q.13	0.151	0.651	0.064	0.002	0.672	0.909	0.121	0.224	0.986	0.071	0.456	0.016	0.04	0.061	0.815	0.197	0.532	0.008	0.116	0.874	0.247
Q.14	0.025	0.116	0.096	0.611	0.519	0.166	0.106	0.014	0.515	0.144	0.869	0.469	0.119	0.329	0.459	0.998	0.185	0.335	0.177	0.395	0.938
Q.15	0.237	0.08	0.096	0.464	0.02	0.881	0.001	0.031	0.779	0.354	0.632	0.44	0.292	0.833	0.869	0.206	0.489	0.696	0.001	0.523	0.983
Q.16	0.024	0.608	0.025	0.078	0.069	0.008	0.18	0.019	0.078	0.3	0.218	0.001	0.312	0.022	0.36	0.533	0.366	0.183	0.872	0.661	0.128
Q.17	0.048	0.352	0.232	0.283	0.061	0.143	0.503	0.021	0.318	0.821	0.57	0.028	0.564	0.892	0.996	0.47	0.572	0.032	0.684	0.974	0.079
Q.18	0.001	0.005	0.02	0.353	0.302	0.005	0.004	<0.001	0.438	0.392	0.802	0.001	0.069	<0.001	<0.001	<0.001	0.105	<0.001	<0.001	0.005	<0.001
Q.19	0.003	0.187	0.005	0.001	<0.001	0.007	0.001	0.11	0.116	0.552	0.117	0.067	0.651	0.029	0.421	0.8	0.03	0.111	0.29	0.635	0.957

Significant association (P<0.01) between the lifestyle-related question and each PFAA are highlighted in grey.

Decrease in PFAA concentrations might be causality or result of loss of appetite. Further clarification would be needed.

There are two limitations in this study. The populations in this study were community dwellers who lived in a rural Japanese area and most of them are elderly. This specific population and

locality could be a bias for the result. Some questions regarding sleep duration, frequency to intake dairy food, snack habit, gait speed, fruit and vegetable intake such as Q. 8, Q. 9, Q. 10, Q. 11, Q. 12, Q. 13 and Q. 14 had little impact to PFAA profiles. This might be related to the specific lifestyle of Japanese rural

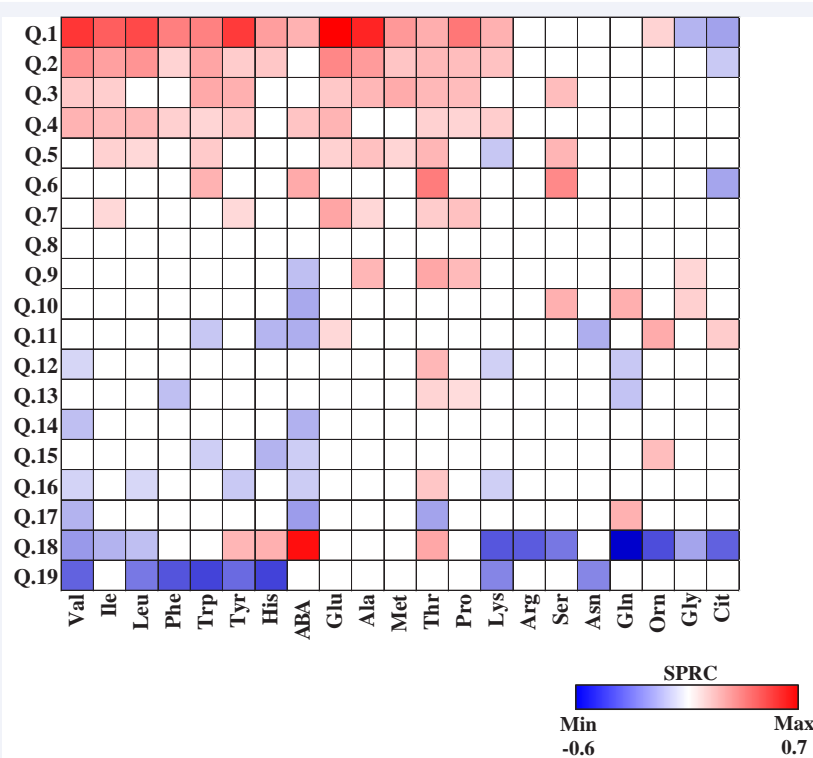


Figure 1 The association between PFAAs and lifestyle habits questionnaire in Japanese community dwellers. Heat map showing the sex-adjusted standardized partial regression coefficients (SPRC) between each plasma free amino acid (PFAA) and the lifestyle-related question is demonstrated. Significantly positive SPRC value ($P < 0.05$) are indicated by red blocks, and significantly negative SPRC values ($P < 0.05$) are indicated by blue blocks. The density represents the absolute values of SPRC. The white blocks represent no significant SPRC values.

community dwellers. Comparison with other populations with different ages and areas are necessary. The second limitation is lack of other blood biochemical variables, medical information, and rigorous nutritional intake records in these participants. In this study, only plasma amino acid concentrations and answers to the questionnaire were available. Although the multiple analyses performed in the study demonstrated a significant relationship between PFAAs and lifestyle questionnaire, further clarification how other possible factors affected the results are to be demonstrated in the future.

CONCLUSION

In conclusion, the present study confirmed the association between the results of a lifestyle habits questionnaire and PFAA profiles. For simple checkup for PFAA alterations, this questionnaire could be a possible initial screening tool for Japanese rural community dwellers.

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CONFLICT OF INTEREST

OK received research grants from Ajinomoto Co., Inc. HJ, KN, AI, YK, TM, MM and TA are employees of Ajinomoto Co., Inc. TK is

a board member of Ajinomoto Co., Inc. The entire financial source was provided by Ajinomoto Co., Inc. No other potential conflicts of interest relevant to this article are declared.

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