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Association between gut microbiota and ultra-processed foods consumption among the patients with type 2 diabetes: a cross-sectional study

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Abstract

Background This study aimed to explore the relationship between ultra-processed foods (UPFs) consumption and gut microbiota in patients with type 2 diabetes (T2D).

Methods This cross-sectional study included 362 participants with T2D. UPFs consumption was assessed using a brief-type self-administered diet history questionnaire, quantified as the density of UPFs intake (g/1000 kcal). Gut microbial composition was evaluated via 16S rRNA gene sequencing. We investigated the association between gut microbiota, previously identified as relevant to T2D, and the density of UPFs intake using Spearman rank correlation coefficients. Multiple regression analysis, adjusting for age, sex, BMI, smoking status, exercise, and medication use, was conducted to further investigate these associations.

Results The mean age of participants was 68 (63–74) years. The density of UPFs intake showed significant associations with *Bifidobacterium* ($r=0.11$, $p=0.031$), *Lactobacillus* ($r=0.11$, $p=0.046$), *Ruminococcus* ($r=-0.12$, $p=0.019$), *Roseburia* ($r=0.11$, $p=0.045$). After adjusting for covariates in multiple regression analysis, *Ruminococcus* and *Roseburia* showed modest negative ($\beta=-0.11$, $p=0.038$) and positive ($\beta=0.12$, $p=0.033$) correlations, with the density of UPFs intake among participants with T2D, respectively.

Conclusions The density of UPFs intake was modestly inversely associated with *Ruminococcus* among patients with T2D and modestly positively associated with *Roseburia*.

Keywords Ultra-processed food consumption, Gut microbiota, Type 2 diabetes

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Background

The growing prevalence of Type 2 diabetes (T2D) is a significant public health concern [1]. It is a chronic disease requiring long-term management, and the global healthcare expenditures related to diabetes have been projected to increase from 2015 to 2030 [2]. Over the past few decades, pharmacological therapy has improved care for patients with T2D [3]; however, nutrition therapy has lagged behind other areas of diabetes research [4].

The global consumption of ultra-processed foods (UPFs) has been rising over recent years [5, 6]. UPFs are industrially manufactured formulations that contain minimal or no whole foods and are composed primarily of industrially-produced ingredients and additives [7]. Consumption of UPFs is associated with increased risk of T2D diabetes, hypertension, cardiovascular disease and all-cause mortality [8–10]. While Visioli et al. [11] showed that not all UPFs are associated with adverse health outcomes, excessive intake of UPFs as a proportion of total energy intake can contribute to health issues. Therefore, the increasing share of UPFs in our diets can raise serious concern for public health, and further research of UPFs is needed.

Diet influences the stability, functionality, and diversity of the gut microbiome [12], which has impacts on metabolism and immune function [13]. Therefore, elucidating the relationship between the gut microbiome and metabolism is essential to prevent diet-related health disorders. Atzeni et al. [14] previously reported a positive correlation between consumption of UPFs and *Alloprevotella*, *Negativibacillus*, *Prevotella*, *Sutterella*, which have been associated with inflammatory gastrointestinal diseases among the patients with overweight or obesity. Additionally, Martinez et al. [15] proposed gut microbiota dysbiosis as a potential clinical marker for neuroinflammation and cognitive decline related to UPFs consumption. These findings highlight the importance of gut microbiota alterations in understanding the mechanisms of various health complications and underscore the need for further investigation in light of rising global UPFs consumption trends.

Previously, we highlighted the dysbiosis among patients with T2D and identified dominant gut microbial genera in Japanese patients with T2D [16]. While several studies have suggested that consumption of UPFs increases the risk of diabetes [17, 18], it remains unclear whether UPFs consumption is associated with gut dysbiosis in the patients with T2D.

In the present study, we investigated the association between gut microbiota and UPFs consumption for Japanese patients with T2D.

Methods

Study participants and data collection

This study received approval from the ethics committee of the Kyoto Prefectural University of Medicine (no. ERB-C-534 and no. RBMR-E-466-5), and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. From November 2016 to December 2017, a total of 523 individuals with available data on gut microbiota from fecal samples were included. This cohort excluded those who had used medications for antibiotics in the past 3 months, those with type 1 diabetes or other forms of diabetes, those without diabetes, and those lacking data of daily energy intake.

Data on medications for dyslipidemia, hypertension, diabetes, and usage of proton pump inhibitors were collected. T2D was diagnosed according to previously reported criteria [19]. Data on body weight (kg), height (cm), body mass index (BMI) (kg/m^2), family history of diabetes and duration of diabetes (years) were recorded for all participants.

Smoking status was determined through a question asking, "Do you currently smoke?" with response choices "yes" or "no." Those who answered "yes" were classified as "smokers," and those who answered "no" as "non-smokers." Consequently, individuals with a history of smoking but who had quit were also categorized as "non-smokers" in this study. Regular exercisers were defined as those who played some type of sport more than once a week [20]. In addition, the participants who drank alcohol daily were defined as drinkers.

Serum creatine (mg/dl), hemoglobin A1c (mmol/mol), fasting plasma glucose (mg/dl), and C-peptide levels (ng/ml) were evaluated using blood samples. The glomerular filtration rate (mL/min/1.73 m^2) was estimated according to the estimation recommended by Japanese Society of Nephrology [21]. C-peptide immunoreactivity index and secretory units of islets in transplantation index were used to evaluate insulin secretion capacity. [22]

Dietary habits were evaluated via a brief-type self-administered diet history questionnaire (BDHQ) [23]. The detail of the BDHQ were fully described elsewhere [24]. In this study, the daily consumption of UPFs (g/day) was evaluated based on dietary intake derived from the BDHQ [25]. The estimation of UPFs was conducted by applying the weight ratios (for example, the weight ratio for “egg” was 4.4%, while for “udon”, it was 7.1%) of each UPFs reported for 147 food codes in prior research by Shinozaki et al. [25] to the weights of individual food items calculated using the BDHQ. Shinozaki et al. [25] pointed out that some food groups in the BDHQ are composed of different food codes. To avoid misestimation in the calculation of UPFs, Shinozaki et al. [25]

did not estimate UPFs intake by categorizing each food item in the BDHQ as UPFs or non-UPFs. Instead, they assigned each food code a probability of UPFs, defined as a weight ratio. Based on nutrient density, daily UPFs intake was adjusted for total daily energy intake [26]. Specifically, the total daily amount of UPFs intake per 1000 kcal was calculated, defined as the density of UPFs intake (g/1000 kcal).

Sampling, DNA extraction, sequencing and data analysis

The detailed methods for fecal sample collection and analysis of gut bacterial composition were published elsewhere [27–29]. Briefly, according to the manufacturer's instructions, genomic deoxyribonucleic acid (DNA) was extracted using the Nucleospin Microbial DNA kit (Macherey-Nagal, Düren, Germany) and purified through the Agencourt AMPure XP (Beckman Couler, Brea, CA, USA) from collected stool samples (fecal collection kit; Techno Suruga lab, Shizuoka, Japan).

We used 16S ribosomal ribonucleic acid (rRNA) metagenomic sequencing to analyze DNA. Sequence libraries from purified DNA samples were generated using a two-step polymerase chain reaction (PCR), with detailed methods available in a previous publication [16], and these libraries were sequenced for 250 paired-end bases using the MiSeq Reagent v3 kit. This process was performed using the MiSeq platform (Illumina, San Diego, CA, USA) at the Biomedical Center at Takara Bio (Shiga, Japan).

The DADA2 plugin within Quantitative Insights Into Microbial Ecology 2 (QIIME2) version 2019.4 was used to generate amplicon sequence variant (ASV) tables, with quality and chimeric variant filtering applied [30]. Taxonomy assignment for each ASV was performed using the Sklearn classifier algorithm with Greengenes database version 13_8 (99% OTU dataset). A total of 6,902 ASVs were identified, excluding five ASVs with a Nearest Sequenced Taxon Index greater than 2.

Statistical analysis

In the previous study, we identified the predominant gut microbial genera among Japanese patients with T2D, with methodology detailed in another publication. [16]

Categorical variables were expressed as numbers and summarized as percentages. Continuous variables were shown as the mean (standard deviations; SD) if normally distributed, as the median (25th, 75th quartile) if not normally distributed. Spearman rank correlation coefficient was used to analyze the association between the density of UPFs intake and the gut microbial composition. Subsequently, multiple regression analysis was performed to calculate the partial regression coefficients (β) and p-values of *Bifidobacterium, Lactobacillus, Ruminococcus, Roseburia,* as these were significantly correlated with the density of UPFs intake. The analysis was adjusted for age, sex, BMI, smoking status, exercise, use of biguanide, alpha-glucosidase inhibitors, potassium-competitive acid blocker, or other proton pump inhibitors. The statistical analyses were performed using JMP Pro 17.2.0 (SAS, Cary, NC, USA). Statistical significance was defined as $p < 0.05$.

Results

Ultimately, all of 362 participants with T2D were included, and 161 participants were excluded, as shown in Fig. 1 (those with type 1 diabetes; $n = 17$, those without diabetes; $n = 115$, those with other diabetes; $n = 8$, those with missing daily energy intake data; $n = 21$). The baseline characteristics of the participants are presented in Table 1. In this study, 199 men and 163 women were included. The mean age was 68 (63–74) years, and the mean BMI was 23.7 (21.5–26.2) kg/m^2.

In addition, the habitual dietary intake data of study participants are shown in Table 2. The mean energy intake was 29.1 (23.8–35.6) kcal/kg IBW/day. The total intake of UPFs was 217.6 (154.3–311.1) g/day, and the density of UPFs intake was 131.8 (101.2–184.7) g/1000 kcal.

In Table 3, we present the correlation between the density of UPFs intake and the gut microbiota composition in participants with T2D. Our findings showed that the density of UPFs intake was positively associated with *Bifidobacterium* ($r = 0.11$, $p = 0.031$), *Lactobacillus* ($r = 0.11$, $p = 0.046$), *Roseburia* ($r = 0.11$, $p = 0.045$), while a negative correlation was observed with *Ruminococcus* ($r = -0.12$, $p = 0.019$). We performed multiple regression analysis for the four types of gut microbiota mentioned above (Table 4). Then, *Ruminococcus* and *Roseburia* respectively showed an association with the density of UPFs intake, after adjusting covariates (age, sex, BMI, smoking status, exercise, use of biguanide, use of alpha-glucosidase and/or inhibitors, use of potassium-competitive acid blocker or proton pump inhibitors). Additionally, we revealed the link between *Ruminococcus* and UPFs intake alone (g/day) for patients with T2D, as shown in Table S1 ($\beta = -0.12$, $p = 0.026$).

Discussion

Our major finding was that *Ruminococcus* and *Roseburia* were associated with the density of UPFs intake for patients with T2D. The density of UPFs intake was negatively associated with *Ruminococcus*, and positively associated with *Roseburia* for these patients.

Previously, Qin et al. [31] described gut microbial dysbiosis in Asian populations with T2D, and Karlsson et al. [32] reported similar findings for European populations.

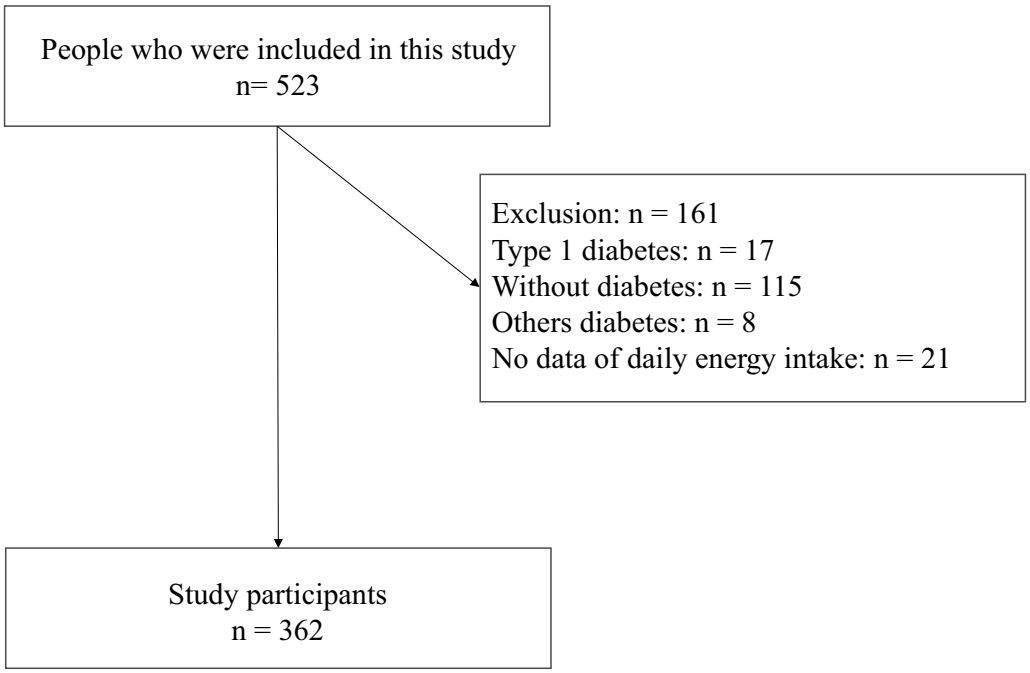

Fig. 1 Flow diagram for the registration of participants

Specifically, T2D is characterized by a reduction in butyrate-producing microbes (e.g., *Ruminococcus, Roseburia,* and *Faecalibacterium prausnitzii*), which results in the promotion of inflammation in the gut [33]. However, among the participants with T2D in our study, we showed negative correlation between the density of UPFs and *Ruminococcus*, while *Roseburia* showed a positive correlation with the density of UPFs. Previous research has shown that UPFs consumption is associated with an increased risk of developing T2D [17], and our findings diverge slightly from the typical gut microbiota profile in these patients. This discrepancy could be attributed to the age of our study participants, with a mean age of 68 years. Park et al. [34] reported an increase in *Roseburia* with aging among Japanese participants, suggesting that the higher proportion of older participants in our study could have influenced our results.

Dietary therapy can significantly contribute to the management of diabetes, as well as exercise and pharmacotherapy. Xu et al. [35] demonstrated that dietary therapy positively impacted metabolic profiles in patients with T2D and this may be mediated through effects on the gut microbiota. Additionally, Zinöcker et al. [36] suggested the potential effects of UPFs on gut microbiota. Previous research indicated a positive association between *Ruminococcus* and carbohydrate intake [37], while carbohydrate intake and dietary fiber intake were negatively associated with UPFs intake [38]. This suggests that carbohydrate, including dietary fiber, may exert a significant influence on the negative correlation between *Ruminococcus* and UPFs consumption observed in the present study. Additionally, *Roseburia* has been reported to be more abundant in patients with T2D following low-carbohydrate dietary interventions that include dietary fiber, compared to those following low-fat diets [39]. Therefore, carbohydrates, including dietary fiber, may contribute to the positive association between *Roseburia* and UPFs, considering the inverse relationship between carbohydrate intake and UPFs. [38]

One of the characteristic ingredients of UPFs is emulsifiers [40]. UPFs containing emulsifiers have been reported to affect the gut microbiota [41], and Salame et al. [42] showed an association between exposure to dietary emulsifiers and T2D. Previous research by Holder et al. [43] demonstrated that dietary emulsifiers induced chronic intestinal inflammation and a reduction in *Ruminococcus*, using female mice. Furthermore, Chassaing et al. [44] showed a reduction in *Ruminococcus* among healthy participants who consumed dietary emulsifiers. This finding suggests that the consumption of dietary emulsifiers may be involved in the negative correlation between UPFs consumption and *Ruminococcus*, as observed in this study.

It is also important to recognize that foods possess various physiological effects beyond the quantification of UPFs, influenced by specific components such as dietary fiber, polyphenols, and probiotic/prebiotic intake. Since polyphenol and probiotic/prebiotic intake cannot

Table 1 Characteristic of study participants

N	ALL *n* = 362
Age, years	68 (63–74)
Men, % (*n*)	55.0 (199)
Duration of diabetes, years	13 (6–20)
Family history of diabetes, % (*n*)	45.0 (163)
Height, cm	160.9 (9.1)
Body weight, kg	61.2 (55–69)
Body mass index, kg/m^2	23.7 (21.5–26.2)
Systolic blood pressure, mmHg	132 (122–144)
Diastolic blood pressure, mmHg	78 (71–85)
Use of antihypertensive drugs, % (*n*)	53.6 (194)
Hypertension, % (*n*)	53.0 (192)
Use of Insulin, % (*n*)	24.3 (88)
Use of SGLT-2 inhibitors, % (*n*)	16.3 (59)
Use of GLP-1 agonist, % (*n*)	16.0 (58)
Use of Biguanide, % (*n*)	41.2 (149)
Use of Alpha-Glucosidase inhibitors, % (*n*)	12.7 (46)
Use of Sulfonylurea, % (*n*)	23.2 (84)
Use of DPP-4 inhibitors, % (*n*)	52.2 (189)
Use of Thiazolidine, % (*n*)	3.9 (14)
Use of P-CAB or PPI, % (*n*)	7.2 (26)
Smoker, % (*n*)	14.4 (52)
Exerciser, % (*n*)	48.9 (177)
Drinker, % (*n*)	67.4 (244)
HbA1c, mmol/mol	53.5 (48.6–60.6)
Plasma glucose, mg/dL	137 (116–166)
C-peptide, ng/mL	1.6 (1.1–2.5)
C-peptide index	1.1 (0.8–1.5)
Serum creatine, mg/dl	0.7 (0.6–0.9)
eGFR, mL/min/1.73 m^2	69.5 (19.4)

Data were presented as mean (standard deviation, or percentage) if normally distributed and median (25% quartile-75% quartile) if not normally distributed, or absolute number

SGLT-2, Sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase 4; P-CAB, potassium-competitive acid blocker; and PPI, proton pump inhibitors

Table 2 Habitual diet intake of study participants

	All *n* = 362
Total energy intake, kcal/day	1663.2 (1320.9–2058.7)
Energy intake, kcal/kg IBW/day	29.1 (23.8–35.6)
Total protein intake, g/day	66.8 (54.9–85.4)
Protein intake per energy intake, %	16.3 (14.3–18.9)
Animal protein intake, g/day	40.7 (29.9–54.1)
Vegetable protein intake, g/day	26.9 (21.3–33.0)
Total Fat intake, g/day	51.6 (39.7–65.6)
Fat intake per energy intake, %	28.6 (6.3)
Total Carbohydrate intake, g/day	213.1 (161.7–259.0)
Carbohydrate intake per energy intake, %	50.8 (8.8)
Ultra-processed food intake, g/day	217.6 (154.3–311.1)
Density of UPFs intake, g/1000kal	131.8 (101.2–184.7)

Data were presented as mean (standard deviation, or percentage) if normally distributed and median (25% quartile-75% quartile) if not normally distributed, or absolute number. Density of UPFs intake, daily Ultra-processed foods intake per daily total energy intake

IBW, ideal body weight,

be evaluated by BDHQ, we investigated the association between dietary fiber intake and *Ruminococcus* or *Roseburia* and found no relationship between dietary fiber intake and *Ruminococcus* ($r = -0.0008$, $p = 0.988$) or *Roseburia* ($r = -0.05$, $p = 0.338$). Therefore, although the evaluation of UPFs is critical in clinical practice, we should consider the food components when designing the dietary intervention, even though no significant correlation was found with dietary fiber.

The high intake of UPFs has been associated with increased risk for various adverse health outcomes [10], including T2D [42] and mortality risk [45], as UPFs consumption has been increasing globally [46]. Martini et al. [47] showed that up to 80% of total calorie intake was derived from UPFs consumption, primarily from sweets and sugar-containing beverages in the United States and Canada. However, a reduction in UPFs consumption has been reported to potentially reduce cardiovascular diseases [48], and Walker et al. [49] reported that lifestyle interventions reduced UPFs consumption, impacting treatment and prevention of metabolic syndrome. Therefore, the reduction in UPFs consumption is necessary worldwide in the future [50]. Moreover, further investigation is required to explore the effects of reducing UPFs consumption on the gut microbiota.

The limitations of this study are outlined below. First, the current study did not demonstrate a causal relationship between UPFs consumption and the gut microbiota. Secondly, our study included only Japanese patients, and the influence of ethnicity and race remains consideration. The gut microbiota composition has been reported to vary among different races and ethnicities [51], and the caution is warranted when generalizing our findings. Thirdly, the multiple regression analysis conducted in the current study did not include comorbidities, dietary fiber intake, probiotic consumption, or supplement use as covariates, and these factors may represent potential limitations. Even after adjusting for all these factors in the regression analysis, residual confounding may still exist. Fourth, in the multiple regression analysis of the current study, the association between UPFs and *Ruminococcus* or *Roseburia* demonstrated relatively small β-values, with p-values nearing the 0.05 threshold. These findings could be influenced by either confounding factors or the sample size.

Table 3 Correlation coefficient between the gut microbiota and the density of UPFs intake

Genera	r	*p*-value
p_Bacteroidetes f_Bacteroidaceae g_Bacteroides	−0.03	0.622
p_Actinobacteria f_Bifidobacteriaceae g_Bifidobacterium	0.11	0.031*
p_Firmicutes f_Ruminococcaceae g_Faecalibacteriumu	−0.08	0.125
p_Bactereroidetes f_Prevptellaceae g_Prevotella	0.01	0.802
p_Actinobacteria f_Coriobacteriaceae g_Collinsella	0.10	0.059
p_Firmicutes f_Lactobacillaceae g_Lactobacillus	0.11	0.046*
p_Firmicutes f_Streptococcaceae g_Streptococcus	0.02	0.649
p_Firmicutes f_Lachnospiraceae g_Blautia	−0.001	0.981
p_Firmicutes f_Ruminococcaceae g_Ruminococcus	−0.12	0.019*
p_Firmicutes f_Veillonellaceae g_Megamonas	0.07	0.161
p_Firmicutes f_Lachnospiraceae g_[Ruminococcus]	0.02	0.773
p_Bacteroidetes f_Porphyromonadaceae g_Parabacteroides	0.02	0.657
p_Firmicutes f_Lachnospiraceae g_Roseburia	0.11	0.045*
p_Firmicutes f_Lachnospiraceae g_Other	−0.05	0.370
p_Firmicutes f_Lachnospiraceae g_Dorea	−0.05	0.367
p_Firmicutes Unclassfied f_Lachnospiraceae	0.02	0.764
p_Firmicutes f_Lachnospiraceae g_Lachnospira	−0.05	0.301
p_Firmicutes f_Erysipelotrichaceae g_[Eubacterium]	0.02	0.729

* significant at $p < 0.05$

Table 4 Univariate and multiple regression analysis on the density of UPFs intake (g/1000 kcal)

	g_Bifidobacterium		*g_Lactobacillus*		*g_Ruminococcus*		*g_Roseburia*	
	β	*p*-value	*β*	*p*-value	*β*	*p*-value	*β*	*p*-value
Age	−0.12	0.020*	0.03	0.633	0.13	0.027*	0.04	0.480
Sex	−0.05	0.307	0.04	0.406	−0.03	0.579	−0.04	0.518
BMI	0.07	0.177	−0.04	0.401	−0.08	0.164	0.12	0.030*
Smoking status	0.02	0.618	0.02	0.654	−0.0002	0.997	−0.05	0.371
Exercise	0.004	0.931	0.03	0.458	0.01	0.848	0.08	0.132
Use of BG	0.05	0.328	0.09	0.077	0.04	0.433	−0.05	0.379
Use of α-GI	−0.48	< 0.0001**	−0.47	< 0.0001**	0.16	0.0029**	0.15	0.003**
Use of P-CAB or PPI	0.007	0.886	−0.16	0.0005**	−0.04	0.494	0.03	0.584
Density of UPFs intake	0.06	0.249	−0.01	0.791	−0.11	0.038*	0.12	0.033*
Density of UPFs intake (Crude)	0.09	0.071	0.02	0.717	−0.16	0.003**	0.10	0.071

Density of UPFs intake, daily Ultra-processed foods intake per daily total energy intake; Multivariate regression analysis was adjusted age, sex, BMI, smoking status, exercise, use of BG, use of α-GI, Use of P-CAB or PPI and Density of UPFs intake (g/1000 kcal)

BMI, Body mass index; BG, biguanide; α-GI, alfa-glucosidase inhibitors; P-CAB, potassium-competitive acid blocker; PPI, proton pump inhibitors; UPFs, ultra-processed foods

** significant at $p < 0.01$; * significant at $p < 0.05$

Notably, the relatively small sample size in our study could have contributed to instability of the β estimates. Therefore, future studies with larger sample sizes are warranted to provide more robust conclusions. Fifth, the total amount of physical activity was not assessed for participants categorized as exercising. Sixth, in our study, we estimated UPFs intake from the BDHQ based on the methodology reported by Shinozaki et al. [25]. Although the validity of their UPFs calculation method has been previously validated [25], there are limitations associated with using the BDHQ. It is challenging to include all food items using the BDHQ, and the BDHQ may not be applicable for studies involving populations with different regional and cultural dietary habits. However, our study also had strength. To the best of our knowledge, the current study represents the first

investigation into the relationship between UPFs and gut microbiota among patients with T2D.

Conclusions

In conclusion, we showed the association between the gut microbial composition, particularly represented by *Ruminococcus* and *Roseburia*, and the density of UPFs intake in patients with T2D. In the future, further research is needed to focus on elucidating the detailed mechanisms and causal relationships between UPFs consumption and the gut microbiata.

Abbreviations

UPFs	Ultra-processed foods
T2D	Type 2 diabetes
BMI	Body mass index
BDHQ	Brief-type self-administered diet history questionnaire
DNA	Deoxyribonucleic acid
rRNA	Ribosomal ribonucleic acid
PCR	Polymerase chain reaction
SD	Standard deviations
β	The partial regression coefficient

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00884-y.

Additional file1.

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Author contributions

T.I. conceptualized the present study and conducted the data analysis and wrote the original manuscript. Y.H. conceptualized the present study, collected the data and contributed the discussion. Y.I. and S.K. conducted the data analysis and contributed the discussion. A.K., R.S. and T.O. collected the data and contributed the discussion. R.I. conducted the data analysis and contributed the discussion. S.K., K.M., K.U. and T.T. conceptualized the present study, collected the data and contributed the discussion. Y.N. conceptualized the present study, performed funding acquisition, collected the data and contributed the discussion. M.H. and M.F. collected the data, contributed the discussion and supervised this study. All authors reviewed and approved the revised manuscript.

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Availability of data and materials

The sequence data used in this study have been submitted to Sequence Read Archive (SRA) with the accession number PRJNA766337 (Available from 1 November 2021).

Declarations

Ethics approval and consent to participate

The present study received approval by the ethics committee of the Kyoto Prefectural University of Medicine (no. ERB-C-534 and no. RBMR-E-466-5), and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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