Nutrition 58 (2019) 69–76

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Basic nutritional investigation

Influence of Japanese diet consumption during pregnancy and lactation on lipid metabolism in offspring

Haruna Ishikawa Ms. [a], Xiaoxu Guo Ms. [a], Saeko Sugawara Ph.D. [a], Yui Iwagaki Ms. [a], Kazushi Yamamoto Mr. [a], Ai Konno Ms. [b], Mika Nishiuchi Ms. [c,d], Tsuyoshi Tsuduki Ph.D. [a,*]

[a] *Laboratory of Food and Biomolecular Science, Graduate School of Agriculture, Tohoku University, Sendai, Japan*
[b] *Department of Nutrition, Sendai Cardiovascular Center, Sendai, Japan*
[c] *Laboratory of Nutrition, Graduate School of Agriculture, Tohoku University, Sendai, Japan*
[d] *Department of Human Health and Nutrition, Shokei Gakuin University, Natori, Japan*

ARTICLE INFO

Article History:
Received 16 September 2017
Received in revised form 26 May 2018
Accepted 10 June 2018

Keywords:
Japanese diet
Pregnancy
Lactation
Offspring
Lipid metabolism

ABSTRACT

Objective: Previous studies have demonstrated that obesity is rare among those who consume the Japanese diet because of its lower caloric content compared with the American diet. Meanwhile, it has been reported that maternal caloric restriction, which induces antiobesity effects, during pregnancy and lactation increases the likelihood of a low birthweight infant, which increases the risks for obesity and diabetes later in life. The aim of this study was to examine the influence of maternal consumption of the Japanese diet during pregnancy and lactation on the risk for obesity and diabetes in the offspring later in life.
Methods: Pregnant mice were divided into three groups and fed either a control diet, Western diet, or Japanese diet, and their offspring were raised until 7 wk old.
Results: Examinations of 18-d-old and 7-wk-old offspring showed no effect of consistently eating a Japanese diet during pregnancy and lactation on the health conditions of 18-d-old offspring, but 7-wk-old offspring showed a decrease in visceral fat and liver triacylglycerol levels. In addition, 7-wk-old offspring from mothers who consumed the Japanese diet during pregnancy and lactation showed a decrease in the homeostatic model assessment of insulin resistance and a reduced risk for developing diabetes. This tendency was also confirmed in 18-d-old offspring. Evaluation of the mechanism revealed that fatty acid synthesis in the liver of the offspring was suppressed by the mother's consumption of the Japanese diet.
Conclusion: From these results, maternal consumption of the Japanese diet during pregnancy and lactation did not adversely affect the offspring, and continual intake of this diet reduced the risk for developing obesity and diabetes in the offspring later in life.

Introduction

Japan has had one of the highest life expectancies in the world since the 1980s [1]. The influence of the Japanese diet on the longevity of the Japanese population is considered to be extremely high. The Japanese diet has lower fat and caloric contents compared with the Western diet and is associated with a high intake of shellfish and other fish and vegetables. In addition, many foods in the Japanese diet, including fermented foods, seaweeds, and green tea, are thought to have high health benefits. Thus, the functionality of the foods comprising the Japanese diet has been well studied worldwide [2–4]. However, to our knowledge the functionality of the Japanese diet itself has hardly been investigated. We have conducted various studies on the Japanese diet itself. In a previous study, we created 1-wk menus of the modern Japanese diet and the modern American diet based on dietary intake surveys conducted in each country; the meals were prepared, freeze-dried, powdered, and then fed to rats to examine the effects on health [5]. A DNA microarray analysis of comprehensive liver gene expression showed that the levels of stress-response genes were lower and those of energy-, glucose-, and lipid metabolism-related genes higher in rats fed the modern Japanese diet compared with those fed the modern American diet. This suggested that the Japanese diet decreases stress and is less likely to cause obesity by stimulating metabolism compared with the modern American diet. In

This research was supported by grants from the Project of the NARO Bio-oriented Technology Research Advancement Institution (Advanced integration research for agriculture and interdisciplinary fields) and The Canon Foundation.
* Corresponding author: Tel: +81 to 22 to 757 to 4392. Fax: +81 to 22 to 757 to 4392.
E-mail address: tsudukit@tohoku.ac.jp (T. Tsuduki).

https://doi.org/10.1016/j.nut.2018.06.006
0899-9007/

addition, DNA microarray analysis showed that the Japanese diet exerts similar effects to those of caloric restriction. The study provided a scientific basis for the value of the Japanese diet in maintaining health.

According to the Developmental Origins of Health and Disease hypothesis that malnutrition or overnutrition in the mother during the pregnancy and lactation periods results in a predisposition for metabolic syndrome development in the offspring later in life, food intake during pregnancy and lactation has a significant influence on the future health of offspring, and various studies on this topic have been carried out worldwide [6–8]. It has been reported that obesity and insulin resistance (IR) tend to occur in low birthweight infants whose mothers underwent caloric restriction during lactation [9–11]. However, caloric restriction is also important for health maintenance. The reported effects of calorie-restricted diets include obesity prevention, activation of lipid metabolism–related genes, and life-span extension because of the decrease in the incidence of aging-related diseases [12,13]. Therefore, whether the Japanese diet with antiobesity effects similar to calorie-restricted diets, ingested by a mother during pregnancy and lactation is more likely to result in low birthweight infants and to increase the risk for metabolic syndrome in the offspring later in life were interested. In this study, the aim was to examine the influence of maternal consumption of the Japanese diet during pregnancy and lactation on the risk for obesity and diabetes in the offspring later in life.

Materials and methods

Preparation of the experimental diets

To determine the effect on offspring of mother's intake of the Japanese diet during pregnancy and lactation, the diet in Japan since 2010 was defined as the modern Japanese diet. Meals were prepared as reported previously [14,15]. Weekly menus (for 21 meals total) based on the 2010 National Nutrition Survey and the National Health and Nutrition Survey in Japan under the guidance of a registered dietitian were created (Table 1) [16,17]. In brief, the menus that the Japanese had eaten on average in 2010 were prepared. The meals were then prepared based on the menus, freeze-dried in a vacuum freeze dryer (FD-550 R; Tokyo Rikakikai, Tokyo, Japan), and homogenized by grinding and stirring. The nutritional composition (protein, fat, carbohydrate, moisture, ash, and energy) of the prepared meals was determined as follows: Proteins were measured by the modified Dumas method, fats by acid digestion, moisture content by vacuum oven drying, ash content by the direct ashing method, and carbohydrates by subtracting the fat, protein, moisture, and ash contents from the total contents. The energy content was calculated by applying modified Atwater factors (4, 9, and 4 kcal/g for protein, fat, and carbohydrate, respectively) [14,18]. To avoid any influence of differences in the mouse diet properties (like sticky), the Japanese diet comprised the normal diet (98121701 M; Research Diets Inc., New Brunswick, NJ, USA) supplemented with 30% of the Japanese diet by weight. Supplementary information on the experimental diets is shown in Supplementary Tables 1 and 2.

Animals

The modern Japanese diet or the Western diet imitating the American high-fat diet were fed dams during pregnancy and lactation. To exclude the possibility that differences between the offspring's postweaning diet and the maternal diet induce metabolic stress to the offspring and adversely affect growth, the same diet as the mother's was given to the offspring postweaning. The effects on lipid metabolism in postnatal offspring were determined by measuring serum and liver parameters and measuring gene expression in the liver. Furthermore, the lipid metabolism of the offspring during the lactation period, during which the mother's diet has the greatest influence on her offspring, was examined similarly. All procedures were performed in accordance with the Animal Experiment Guidelines of Tohoku University, and the animal protocol was approved by the Animal Use Committee at Tohoku University. Female Institute of Cancer Research (ICR) mice on the fourth day of pregnancy were purchased from Japan CLEA (Tokyo, Japan). Mice were maintained in a room at a constant temperature (24 ± 1°C) and humidity under a 12:12 h light-to-dark cycle. Dams were randomly divided into three groups as follows: the control (CO) group, fed a normal diet; a high-fat diet (HD) group, fed a Western diet (D12079 BM; Research Diet Inc.); and a Japanese diet (JD) group, fed the prepared Japanese diet (Supplementary Tables 1 and 2). Dams were provided free access to water and chow. In experiment 1, the offspring were weaned at 3 wk old, and 10 male offspring from each group were fed the same diet as their mothers (Fig. 1). After weaning, the food intake of the offspring was measured every 3 d and the body weight every week. As in our previous study, after 12 h of fasting, the offspring were weighed and sacrificed at 7 wk of age, and blood, brain,

Table 1
Menu card of the Japanese diet

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Breakfast	Toast Cafe au lait Salad Banana	Rice Miso soup Natto (fermented soybeans) Simmered dish	Rice Miso soup Ham and eggs Simmered *Hijiki*seaweed	Toast Scrambled eggs Salad Cafe au lait Juice	Pancake Vegetable Juice Fruit Yogurt Coffee	Rice Sunny-side up egg Blue rosies saute Food Boiled in soy sauce Miso soup Kelp tea	Rice Grilled fish Dipping Pickles Apple Tea
Lunch	*Tororo* Soba with spicy soy sauce added Grilled seafood Boiled beans	Curry and rice Mandarin orange Yogurt	Rice Fried vegetables Soy milk Watermelon	Fried rice Marinated bean sprouts Chinese soup Grape Cider	Rice White fish meuniere Marinated Simmered sweet potatoes with boiled apple	Beef over rice bowl Coffee Carbonated juice	Rice Tofu with meat miso Starchy sauce Seaweed salad Clear soup Roasted green tea
Snack	Sweet bread Tea Instant Chinese noodles	Donut Coffee	Barley tea Cola	Candy	Steamed bun	Chocolate Black tea	Biscuits
Dinner	Rice Marinated horse mackerel, *Nanban*-Style Cooked beans with various vegetables Miso soup	Rice Hot pot Dish dressed with sesame sauce Kimchi	Pizza Rice ball Grilled chicken Sashimi Popcorn Salad	Rice Braised meat and vegetables *Mozuku* with vinegar Miso soup	Rice Miso soup Grilled meat Simmered dish	Fried noodles Pickled spinach dipped in sauce	Pasta Salad Milk soup Coffee Sherbet

Table 2
Primer pairs used for quantitative reverse-transcription polymerase chain reaction analysis

NM_031884	*Abcg5*	Forward	AGGGCCTCACATCAACAGAG
		Reverse	GCTGACGCTGTAGGACACAT
NM_153151	*Acat3*	Forward	CCAGTGGTCATCGTCTCGG
		Reverse	GGACAGGGCACCATTGAAGG
NM_133904	*Acc*	Forward	CGCTCACCAACAGTAAGGTGG
		Reverse	GCTTGGCAGGGAGTTCCTC
NM_015729	*Acox1*	Forward	TCCAGACTTCCAACATGAGGA
		Reverse	CTGGGCGTAGGTGCCAATTA
NM_007393	*β-actin*	Forward	GGCTGTATTCCCCTCCATCG
		Reverse	CCAGTTGGTAACAATGCCATGT
NM_009948	*Cpt1*	Forward	ATTCTGTGCGGCCCTTATTGGAT
		Reverse	TTTGCCTGGGATGCGTGTAGTGT
NM_009949	*Cpt2*	Forward	TGTCTTCCAAGCACTTCTGG
		Reverse	TGGATAGGCTGCAATGTCTC
NM_007824	*Cyp7 a1*	Forward	CAAGTGTCCCCCTCTAGA
		Reverse	ACTCAATATCATGTAGTGGTGGCAAA
NM_007988	*Fasn*	Forward	CCTGGATAGCATTCCGAACCTG
		Reverse	TTCACAGCCTGGGGTCATCTTTGC
NM_008062	*G6 pdx*	Forward	TGGGTCCACCACTGCCACTTTTG
		Reverse	ATTGGGCTGCACACGGATGACCA
AK079302	*HMG-CoAR*	Forward	AGCTTGCCCGAATTGTATGTG
		Reverse	TCTGTTGTGAACCATGTGACTTC
NM_013839	*Lxra*	Forward	CTCAATGCCTGATGTTTCTCCT
		Reverse	TCCAACCCTATCCCTAAAGCAA
M29546	*Me*	Forward	CCTCACCACTCGTGAGGTCAT
		Reverse	CGAAACGCCTCGAATGGT
NM_011144	*Pparα*	Forward	AACATCGAGTGTCGAATATGTGG
		Reverse	AGCCGAATAGTTCGCCGAAAG
NM_009270	*Sqle*	Forward	ATTGGCTCAGGCCTTGTATG
		Reverse	ATTGAAAGCAACCCAACAGG
NM_011480	*Srebp1 c*	Forward	GGAGACATCGCAAACAAGC
		Reverse	TGAGGTTCCAAAGCAGACTG

Abcg5, ATP-binding cassette, subfamily G (WHITE), member 5; *Acat3,* acetyl-coenzyme A acetyltransferase 3; *Acc,* acetyl-coenzyme A carboxylase beta; *Acox1,* acyl-coenzyme A oxidase 1, palmitoyl; *β-actin,* actin, beta, cytoplasmic; *Cpt1,* carnitine palmitoyl transferase 1; *Cpt2,* carnitine palmitoyltransferase 2; *Cyp7 a1,* cytochrome P450, family 7, subfamily a, polypeptide 1; *Fasn,* fatty acid synthase; *G6 pdx,*glucose-6-phosphate dehydrogenase X-linked; *HMG-CoAR,* 3-hydroxy-3-methylglutaryl-coenzyme A reductase; *Lxra,* nuclear receptor subfamily 1, group H, member 3; *Me,* malic enzyme; *Pparα,* peroxisome proliferator activated receptor alpha; *Sqle,* squalene epoxidase; *Srebp1 c,* sterol regulatory element binding protein 1 c.

liver, kidney, pancreas, and white adipose tissue (WAT) samples were collected [19]. Blood was centrifuged (900 *g* at 5°C for 15 min) to prepare serum. The serum and organs were stored at −80°C until the assays were performed. In experiment 2, to investigate the influence of the mother's modern Japanese diet during pregnancy and lactation on the infants (Fig. 1), the offspring were evaluated at 18 d of age before weaning. After fasting for 12 h, the 18-d-old offspring were sacrificed, and blood, liver, and WAT samples were collected. Samples were prepared and stored in the same manner until use.

Biochemical analyses of serum and liver

The lipid compositions in serum and liver were measured as described previously [20]. Serum and liver triacylglycerol (TG) and total cholesterol (TC) levels and serum phospholipid (PL) and glucose levels were measured using commercial enzyme kits (Wako Pure Chemical, Osaka, Japan). Serum insulin levels were determined using an ELISA kit (Morinaga Institute of Biological Science, Kanagawa, Japan). However, as the volume of serum collected from 18-d-old mice was small, the serum glucose and insulin levels were measured by pooling equal amounts of samples from each group. Liver PL levels were determined using a method described by Rouser et al. [21].

Histologic analysis

To observe WAT tissue and liver in greater detail, histologic analyses were performed as described previously [20,22]. Liver and epididymal adipose tissues were fixed in 10% formalin and embedded in paraffin. Vertical sections (5 μm thick) were cut, mounted on glass slides, stained with hematoxylin and eosin, and observed under a microscope (BZ-9000; Keyence, Osaka, Japan). In this study, the adipocyte size and the lipid accumulation in hepatocyte were observed. The mean area of the adipocyte size was determined at 100 × magnification using a microscope (BZ-9000). To ensure the accuracy of measurements, we averaged 30 measurements for each animal. Measurements were obtained from 10 animals per group. Data are presented as the mean ± SD for each group [20,22,23].

Messenger RNA expression analysis

The differences in lipid accumulation in WAT and liver among the groups may have been due to a difference in lipid metabolism in liver. Thus, the expression levels of lipid metabolism–related genes in the liver were measured by quantitative reverse-transcription polymerase chain reaction (qRT-PCR). For qRT-PCR, total RNA was isolated from the liver using the RNeasy Mini Kit (Qiagen, Valencia, CA, USA) as described previously [20,22] and stored at −80°C until the assays were performed. cDNA was reverse transcribed from the RNA using the PrimeScript RT Master Mix (Takara Bio, Otsu, Japan), and messenger RNA (mRNA) levels were quantified using the Thermal Cycler Dice Real Time System (Takara Bio) [20,22]. The primer sequences, based on previous reports, were designed by Sigma-Aldrich (Tokyo, Japan; Table 2) [24–26]. The expression levels were normalized to the β-actin expression level and expressed relative to the control sample.

Statistical analysis

Results are expressed as the mean ± SD. Data were analyzed by one-way analysis of variance, followed by the Tukey–Kramer test for multiple comparisons among the three groups. A difference was considered significant at $P < 0.05$. In addition, the effect size (η^2) of the result with the significant difference was shown. The effect size was evaluated as follows: 0.01 to 0.06 is small, 0.06 to 0.14 is medium, and greater than 0.14 is large [27]. These statistical analyzes were done using BellCurve for Excel (Social Survey Research Information Co., ltd., Tokyo, Japan).

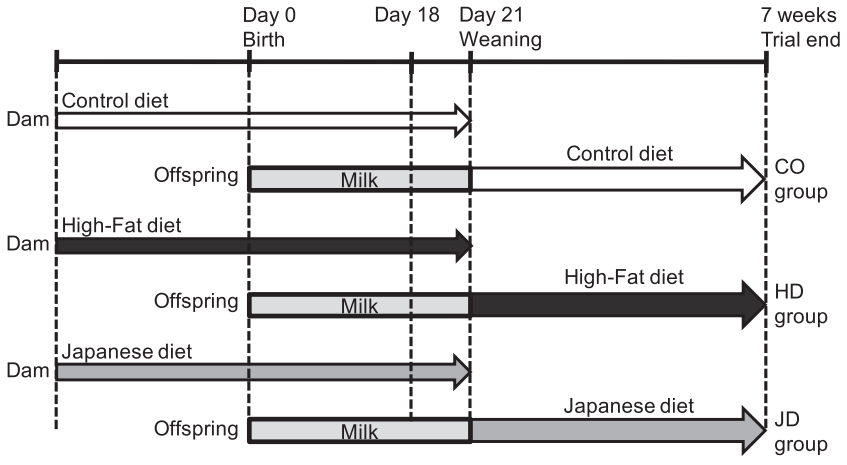

Fig. 1. Study protocol. Postnatal dams were given experimental diets (control diet, high-fat diet, or Japanese diet) and all offspring were given the same experimental diets as their mother after weaning at 3 wk.

Results

Compositions of the experimental diets

The nutritional compositions of the experimental diets are presented in Table 3. The proportion of protein was higher in the Western diet but comparable to the Japanese diet compared with the control diet. The proportion of fat was lowest in the control diet, fivefold lower than that in the Western diet. The proportion of fat in the Japanese diet was half that of the Western diet. The proportion of carbohydrates was highest in the control diet and ~20 or 10 g/100 g lower in the Western or Japanese diet than in the control diet, respectively. The energy per 100 g diet was the lowest in the control diet and highest in the Western diet.

Growth parameters

The body weights at 3 and 7 wk were significantly higher in the HD group than in the CO and JD groups (Table 4). The weights of the brain and kidney were significantly higher in the JD group than in the HD group. However, there was no significant difference in the baseline weights. The weight of the liver was significantly higher in the HD group than in the CO and JD groups. There was no significant difference in the weight of the pancreas among the groups. The mesenteric, perinephric, epididymal, and total WAT weights were lowest in the JD group, significantly lower than those in the HD group. Because WAT weights showed a significant difference among the three groups, histologic analysis was performed. Adipocytes were larger in the HD group than in the CO and JD groups (Fig. 2A). In addition, the adipocyte area was significantly larger in the HD group than in the CO and JD groups (Fig. 2B) and showed a decreased tendency in the JD group compared with the CO group ($P = 0.08$). The effect size for this result was large ($\eta^2 = 0.62$).

Biochemical parameters in serum

The serum TC level was significantly higher in the HD group than in the CO and JD groups (Table 5). The effect size for this result was medium ($\eta^2 = 0.12$). The serum insulin level was significantly lower in the JD than HD group. The effect size for this result was small ($\eta^2 = 0.06$). There was no difference in the homeostatic model assessment (HOMA-IR), an index of IR, between the CO and JD groups, but this value in the JD group was 55% that of the CO group. In addition, the HOMA-IR was significantly lower in the JD than HD group. The effect size for this result was small ($\eta^2 = 0.03$). There were no differences in the serum TG, PL, or glucose levels among the three groups.

Biochemical parameters in liver

The liver TG and TC levels were significantly higher in the HD group than in the CD and JD groups (Table 5). The effect sizes for these results were large ($\eta^2 = 0.60$ and 0.63). There was no difference in the liver PL level among the CO, HD, and JD groups. Because the liver TG and TC levels showed a significant difference among the three groups, histologic analysis was performed. Lipid accumulation in hepatocytes in the HD group was observed as indicated by black arrows. We were unable to observe lipid accumulation in hepatocytes in the CO and JD groups (Fig. 2C).

Table 3
Nutrient compositions of the experimental diets

Experimental diets	CO	HD	JD
Protein (g/100 g)	16.6	19.9	16.1
Fat (g/100 g)	4.3	20.8	10.8
Carbohydrate (g/100 g)	71.4	50.3	60.5
Energy (kcal/100 g)	391	468	403

CO, control diet; HD, high-fat diet; JD, Japanese diet.

Table 4
Growth parameters

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD
Initial body weight (g)	11.7 ± 0.7 [a]	15.0 ± 2 [b]	10.5 ± 0.8 [a]
Final body weight (g)	36.7 ± 2.6 [a]	40 ± 3.1 [b]	34.5 ± 1.6 [a]
Body weight gain (g)	25 ± 2.5	25.1 ± 4.6	23.1 ± 1.4
Food intake (g/d)	4.15 ± 0.28	3.77 ± 0.39	3.49 ± 0.64
Energy intake (kcal/d)	16.2 ± 1	17.7 ± 1.8	14 ± 2.6
Tissue weight (g/100 g BW)			
Brain	1.36 ± 0.08 [ab]	1.28 ± 0.12 [a]	1.46 ± 0.05 [b]
Liver	4.09 ± 0.20 [a]	4.72 ± 0.35 [b]	4.03 ± 0.21 [a]
Pancreas	0.85 ± 0.13	0.88 ± 0.08	0.78 ± 0.10
Kidney	1.69 ± 0.24 [ab]	1.64 ± 0.13 [a]	1.83 ± 0.07 [b]
White adipose tissue			
Mesenteric	0.75 ± 0.24 [ab]	0.93 ± 0.38 [b]	0.56 ± 0.19 [a]
Perirenal	0.78 ± 0.36 [ab]	1.01 ± 0.32 [b]	0.59 ± 0.21 [a]
Epididymal	1.53 ± 0.64 [a]	2.58 ± 0.75 [b]	1.36 ± 0.27 [a]
Total	3.06 ± 1.09 [a]	4.52 ± 1.24 [b]	2.50 ± 0.61 [a]

BW, body weight; CO, control diet; HD, high-fat diet; JD, Japanese diet.
Different superscript letters indicate significantly different means at $P < 0.05$.

mRNA levels of lipid metabolism–related genes in the liver

The mRNA level of *Acc*, which promotes fatty acid synthesis, was significantly lower in the HD group than in the CO group (Table 6). The effect size for this result was medium ($\eta^2 = 0.06$). The mRNA level of *Srebp1 c*, which encodes a transcription factor regulating fatty acid synthesis, was lowest in the JD group, significantly lower than that in the HD group. The effect size for this result was medium ($\eta^2 = 0.08$). The mRNA level of *Sqle*, which is involved in cholesterol synthesis, was significantly lower in the HD group than in the CO group. The effect size for this result was medium ($\eta^2 = 0.07$). The mRNA levels of *Acat3* and *Lxra*, which are involved in cholesterol catabolism, were significantly lower in the HD and JD groups than in the CO group. The effect size for these results was large and medium ($\eta^2 = 0.26$ and 0.06). In addition, the mRNA level of *Abcg5*, which is involved in cholesterol catabolism, was significantly higher in the HD group than in the CO and JD groups. The effect size for this result was large ($\eta^2 = 0.54$). There were no significant differences in the mRNA levels of *Fasn*, *Me*, *G6 pdx*, *Acox1*, *Cpt1*, *Cpt2*, *Ppara*, *HMG-CoAR*, or *Cyp7 a1* among the groups.

Growth parameters of the offspring at 18 d of age

The body composition of offspring at 18 d of age to investigate the influence before weaning were examined (experiment 2). There was no significant difference among the CO, HD, and JD groups in terms of body weight, liver weight, or WAT weight at 18 d of age (Table 7). Therefore, consumption of the Japanese diet during pregnancy and lactation did not significantly affect the body composition of the offspring before weaning.

Biochemical parameters in the serum and liver of the offspring at 18 d of age

There was no significant difference in the serum TG, TC, or PL levels among the CO, HD, and JD groups at 18 d of age (Table 8). In

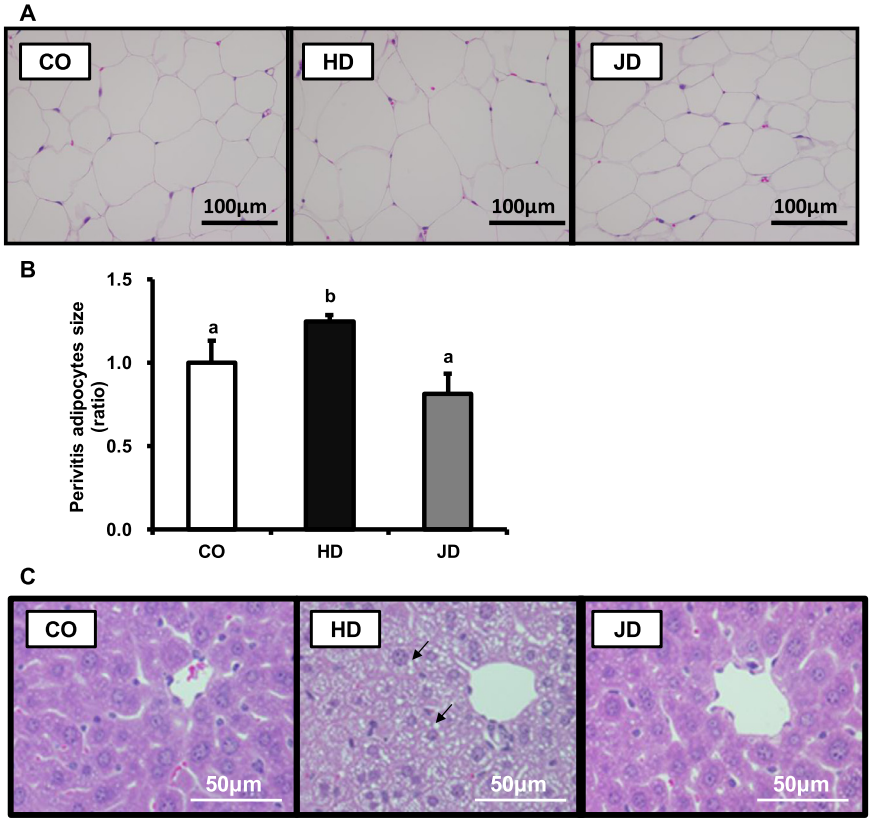

Fig. 2. (**A**) Effects of the Japanese diet intake from pregnancy and lactation on adipocytes of offspring at 7 wk. Photographs were hematoxylin and eosin staining of epididymal adipose tissue sections from representative mice of each group (scale bar = 100 μm). (**B**) Bar graph of the adipocytes size ratio of the CO, HD, and JD group. Values are means ± SD, n = 10. [a,b]Different superscript letters indicate significantly different means at $P < 0.05$. (**C**) Effects of the Japanese diet intake from pregnancy and lactation on liver of offspring at 7 wk. Photographs were hematoxylin and eosin staining of liver sections from representative mice of each group (scale bar = 50 μm). CO, control diet; HD, high-fat diet; JD, Japanese diet.

Table 5
Biochemical parameters

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD
Serum			
TG (mmol/L)	1.22 ± 0.53	0.90 ± 0.28	0.92 ± 0.33
TC (mmol/L)	2.83 ± 0.80 [a]	3.58 ± 0.52 [b]	2.60 ± 0.46 [a]
PL (mmol/L)	13.7 ± 3.1	14.4 ± 2.5	12.2 ± 2.1
Glucose (mmol/L)	5.94 ± 1.39	6.85 ± 1.40	5.72 ± 1.09
Insulin (nmol/L)	0.06 ± 0.04 [ab]	0.06 ± 0.03 [b]	0.02 ± 0.01 [a]
HOMA-IR (ratio)	1.00 ± 0.47 [ab]	1.31 ± 0.54 [b]	0.55 ± 0.28 [a]
Liver			
TG (μmol/g)	61.5 ± 22.4 [a]	140 ± 18.1 [b]	58.7 ± 24.0 [a]
TC (μmol/g)	29.1 ± 9.3 [a]	110 ± 35 [b]	40.2 ± 9.9 [a]
PL (μmol/g)	28.6 ± 11.5	31.1 ± 2.1	35.2 ± 3.2

CO, control diet; HD, high-fat diet; HOMA-IR, homeostatic model assessment of insulin resistance; JD, Japanese diet; PL, phospholipid; TC, total cholesterol; TG, triacylglycerol.
Different superscript letters indicate significantly different means at $P < 0.05$.

addition, the serum glucose and insulin levels were measured; because the volume of serum collected was small, these levels were measured by pooling equal volumes of the individual samples within each group. The serum glucose level was low in the JD group (5.31 mmol/L) compared with the CO (6.87 mmol/L) and HD (6.68 mmol/L) groups, but the insulin level was similar among the CO, HD, and JD groups (CO, 0.05 nmol/L; HD, 0.05 nmol/L; JD, 0.04 nmol/L). The liver TG and PL levels at 18 d of age did not differ significantly between the three groups, but the liver TC level was significantly higher in the HD and JD groups than in the CO group ($P < 0.001$). The effect size for this result was large ($\eta^2 = 0.54$).

mRNA levels of lipid metabolism–related genes in the liver at 18 d of age

The expression of lipid metabolism–related genes in the liver at 18 d of age was measured by qRT-PCR. There was no significant difference in the mRNA levels of *Acc*, *Fasn*, *G6 pdx*, or*Srebp1 c*, which are involved in fatty acid synthesis, but that of *Me* was significantly higher in the JD group than in the CO and HD groups (Table 9). The effect size for this result was large ($\eta^2 = 0.16$). The mRNA levels of *Aco*, *Cpt1*, and *Ppara*, involved in fatty acid β oxidation, did not differ significantly among the three groups. Although the expression of *Cpt2* was significantly lower in the HD group than in the CO group, there was no significant difference in the JD group compared with the other two groups. The effect size for this result was large ($\eta^2 = 0.22$). The expression of *Abcg5*, which is related to cholesterol secretion, was significantly higher in the HD group than in the CO group, but there was no significant difference in the JD group compared with the other two groups. The effect size for this result was large ($\eta^2 = 0.16$). The mRNA levels of *HMG-CoAR*, and *Sqle*, involved in cholesterol synthesis, and *Acat3*, *Cyp7 a1* and *Lxra*,

Table 6
mRNA levels of lipid metabolism–related genes in the liver

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD	Function
(Ratio)				
Acc	1.00 ± 0.53 [b]	0.52 ± 0.22 [a]	0.72 ± 0.23 [ab]	Fatty acid synthesis
Fasn	1.00 ± 0.17	0.98 ± 0.14	0.97 ± 0.22	
G6 pdx	1.00 ± 0.20 [a]	1.30 ± 0.20 [b]	1.32 ± 0.27 [b]	
Me	1.00 ± 0.50	0.95 ± 0.29	1.36 ± 0.67	
Srebp1 c	1.00 ± 0.49 [ab]	1.42 ± 0.68 [b]	0.70 ± 0.19 [a]	
Acox1	1.00 ± 0.47	0.98 ± 0.39	1.08 ± 0.47	Fatty acid β-oxidation
Cpt1	1.00 ± 0.54	1.67 ± 0.52	1.47 ± 0.96	
Cpt2	1.00 ± 0.29	1.02 ± 0.22	1.18 ± 0.42	
Ppara	1.00 ± 0.30	0.90 ± 0.16	0.97 ± 0.35	
HMG-CoAR	1.00 ± 0.12	1.13 ± 0.19	1.29 ± 0.28	Cholesterol biosynthesis
Sqle	1.00 ± 0.58 [b]	0.23 ± 0.03 [a]	0.44 ± 0.10 [ab]	
Abcg5	1.00 ± 0.21 [a]	2.53 ± 0.66 [b]	1.42 ± 0.21 [a]	Cholesterol catabolism
Acat3	1.00 ± 0.17 [b]	0.64 ± 0.14 [a]	0.72 ± 0.16 [a]	
Cyp7 a1	1.00 ± 0.93	1.58 ± 0.82	1.40 ± 0.79	
Lxra	1.00 ± 0.14 [b]	0.79 ± 0.19 [a]	0.89 ± 0.15 [a]	

Abcg5, ATP-binding cassette, subfamily G (WHITE), member 5; *Acat3,* acetyl-coenzyme A acetyltransferase 3; *Acc,* acetyl-coenzyme A carboxylase beta; *Acox1,* acyl-coenzyme A oxidase 1, palmitoyl; *β-actin,* actin, beta, cytoplasmic; CO, control diet; *Cpt1,* carnitine palmitoyl transferase 1; *Cpt2,* carnitine palmitoyltransferase 2; *Cyp7 a1,* cytochrome P450, family 7, subfamily a, polypeptide 1; *Fasn,* fatty acid synthase; *G6 pdx,*glucose-6-phosphate dehydrogenase X-linked; HD, high-fat diet; *HMG-CoAR,* 3-hydroxy-3-methylglutaryl-coenzyme A reductase; JD, Japanese diet; *Lxra,* nuclear receptor subfamily 1, group H, member 3; *Me,* malic enzyme; *Pparα,* peroxisome proliferator activated receptor alpha; *Sqle,* squalene epoxidase; *Srebp1 c,* sterol regulatory element binding protein 1 c.
Different superscript letters indicate significantly different means at $P < 0.05$.

Table 7
Growth parameters of 18-d-old offspring

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD
Body weight (g)	7.16 ± 1.65	8.36 ± 0.56	6.97 ± 1.42
Tissue weight (g/100 g BW)			
Liver	3.73 ± 0.27	3.88 ± 0.39	3.51 ± 0.44
Total white adipose tissue	0.27 ± 0.16	0.32 ± 0.18	0.32 ± 0.19

BW, body weight; CO, control diet; HD, high-fat diet; JD, Japanese diet.

Table 8
Biochemical parameters of 18-d-old offspring

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD
Serum			
TG (mmol/L)	1.15 ± 0.45	0.98 ± 0.21	1.01 ± 0.17
TC (mmol/L)	3.55 ± 0.74	3.92 ± 0.36	3.56 ± 0.55
PL (mmol/L)	17.3 ± 1.3	18.9 ± 2.3	17.7 ± 2.1
Liver			
TG (μmol/g)	44.6 ± 7.3	50.8 ± 11.6	43.1 ± 3.8
TC (μmol/g)	15.4 ± 1.3 [a]	26.4 ± 4.7 [b]	22.5 ± 2.6 [b]
PL (μmol/g)	30.4 ± 2.4	30.6 ± 2.3	32.5 ± 3

CO, control diet; HD, high-fat diet; JD, Japanese diet; PL, phospholipid; TC, total cholesterol; TG, triacylglycerol.
Different superscript letters indicate significantly different means at $P < 0.05$.

related to cholesterol catabolism, did not differ significantly between the three groups.

Discussion

In the present study, whether consumption of the Japanese diet, which is associated with antiobesity effects, by a mother during pregnancy and lactation affects lipid metabolism or increases the risk for developing a lifestyle-related disease later in life in her offspring was investigated. The CO and HD control groups comprised mice fed a normal diet and mice fed a Western diet characteristic of the American diet, respectively. Comparisons of these two groups with the group fed a modern Japanese diet revealed that maternal consumption of the Japanese diet during pregnancy and lactation did not adversely affect lipid metabolism in the infants, and that fat accumulation in the offspring later in life was suppressed by Japanese diet consumption after weaning. In addition, the significantly decreased WAT weight in mice that were fed JD suggested that the maternal and offspring less JD intake induced obesity in the offspring.

In a previous study comparing Japanese and American diets, it was found that the Japanese diet exhibited caloric restriction-like effects and strong health benefits compared with the American diet [5]. Although the modern Japanese diet is more Westernized than the traditional Japanese diet, with a higher lipid composition, the antiobesity effects of the modern Japanese diet are stronger than those of the American diet. The Japanese foods used in this study were prepared based on the 2010 National Health and Nutrition Survey. The menu for the 21 meals per week had the feature that mainly for rice, and meat, milk, oils, fruits and so on are abundantly added to traditional foods such as fish, vegetables, and soybeans, and well represented the Japanese diet [16]. In addition, in a recent study, differences in the energy balance of proteins, lipids, and carbohydrates among the 1960, 1975, 1990, and 2005 typical Japanese diets were compared and the health benefits of these diets were reviewed. Our results suggested that the difference in health benefits among Japanese diets of different generations did not depend on the balance among proteins, lipids, and carbohydrates [14]. Therefore, it was considered that the results obtained in this study were attributed to the ingredients of the Japanese diet.

The offspring of dams undergoing moderate caloric restriction during pregnancy showed no significant change in body weight at weaning compared with offspring from mothers consuming a normal diet during pregnancy. However, offspring born from a calorie-restricted mother had significantly higher body weight compared with offspring from mothers consuming a normal diet during pregnancy, although they took the same normal diet after weaning

Table 9
mRNA levels of lipid metabolism–related genes in the liver of 18-d-old offspring

	CO (n = 10) means ± SD	HD (n = 10) means ± SD	JD (n = 10) means ± SD	Function
(Ratio)				
Acc	1.00 ± 0.26	2.04 ± 1.45	0.63 ± 0.17	Fatty acid synthesis
Fas	1.00 ± 0.30	1.41 ± 0.87	0.79 ± 0.31	
G6 pdx	1.00 ± 0.73	1.10 ± 0.77	0.87 ± 0.16	
Me	1.00 ± 0.43 [a]	0.99 ± 0.26 [a]	1.87 ± 0.80 [b]	
Srebp1 c	1.00 ± 0.45	1.00 ± 0.39	0.66 ± 0.25	
Aco	1.00 ± 0.21	0.73 ± 0.31	0.92 ± 0.46	Fatty acid β-oxidation
Cpt1	1.00 ± 0.30	1.17 ± 0.45	1.53 ± 0.99	
Cpt2	1.00 ± 0.08 [b]	0.60 ± 0.22 [a]	0.76 ± 0.22 [ab]	
Ppara	1.00 ± 0.23	0.89 ± 0.33	0.97 ± 0.32	
HMG-CoAR	1.00 ± 0.28	0.87 ± 0.49	0.80 ± 0.13	Cholesterol biosynthesis
Sqle	1.00 ± 0.54	0.85 ± 0.87	0.24 ± 0.13	
Abcg5	1.00 ± 0.40 [a]	2.02 ± 0.89 [b]	1.53 ± 0.16 [ab]	Cholesterol catabolism
Acat3	1.00 ± 0.22	0.84 ± 0.31	1.27 ± 0.55	
Cyp7 a1	1.00 ± 0.35	1.57 ± 0.71	2.07 ± 1.48	
Lxra	1.00 ± 0.28	0.87 ± 0.49	0.80 ± 0.13	

Abcg5, ATP-binding cassette, subfamily G (WHITE), member 5; *Acat3*,acetyl coenzyme A acetyltransferase 3; *Acc*, acetyl-coenzyme A carboxylase beta; *Acox1*,acyl-coenzyme A oxidase 1, palmitoyl; *β-actin*, actin, beta, cytoplasmic; CD, control diet; *Cpt1*,carnitine palmitoyl transferase 1; *Cpt2*,carnitine palmitoyl transferase 2; *Cyp7 a1*,cytochrome P450, family 7, subfamily a, polypeptide 1; *Fasn*, fatty acid synthase; *G6 pdx*,glucose-6-phosphate dehydrogenase X-linked; HD, high-fat diet; *HMG-CoAR*, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; JD, Japanese diet; *Lxra*, nuclear receptor subfamily 1, group H, member 3; *Me*, malic enzyme; *Pparα*, peroxisome proliferator activated receptor alpha; *Sqle*, squalene epoxidase; *Srebp1 c*,sterol regulatory element binding protein 1 c.
Different superscript letters indicate significantly different means at $P < 0.05$.

[28]. In addition, caloric restriction during pregnancy and lactation induces nutritional deficiencies in the fetus, which affects the growth process of the fetus and promotes greater absorption of energy. And, when the offspring ingest a normal or high-energy diet after weaning, accumulation of visceral fat and excessive weight gain occur [9,29,30]. In the present study, offspring from the JD group did not exhibit significant change in body weight at 18 d old, but at 7 wk old, they exhibited the lowest body weight of the three groups, significantly lower than that of offspring from the HD group. The WAT weight of the offspring did not differ significantly among the three groups at 18 d of age, but at 7 wk of age, the visceral fat weight of the offspring was lowest in the JD group and significantly lower compared with the HD group. Therefore, maternal consumption of the Japanese diet, unlike caloric restriction, did not lead to increased body weight or visceral fat in the offspring later in life, even if the diet was consumed during pregnancy and lactation. In addition, in this study, no difference was observed between the maternal diet and postweaning offspring diet, and thus no stress owing to changes in energy or the various dietary ingredients was induced from pre- to postweaning, which was one of the factors that adversely affect offspring.

It was reported that offspring born from mothers undergoing moderate caloric restriction during pregnancy exhibit significantly higher serum insulin levels and HOMA-IR values, indicators of IR, compared with offspring born from mothers consuming a normal diet during pregnancy [31]. Therefore, maternal caloric restriction caused IR in her offspring, which is thought to be a factor in the development of diabetes later in life. In this study, the glucose and insulin levels of the JD group offspring at 18 d and even at 7 wk of age were the lowest among all three groups and were significantly lower than those of the HD group offspring. The value of HOMA-IR of the JD group offspring was the lowest among all three groups and significantly lower than that of the HD group offspring. Thus, ingestion of the Japanese diet by a mother during pregnancy and lactation was considered to prevent IR in the offspring and to reduce the risk for developing diabetes later in life.

The TG level in the liver of the JD group offspring was the lowest among all three groups, significantly lower than that of the HD group offspring. Therefore, lipid metabolism in the liver of the offspring was considered- to be different among the groups. At 18 d old, the expression of *Me*, which is associated with fatty acid synthesis [32], was significantly higher in offspring from the JD group than in those from the CD and HD groups. However, the high expression of *Me* in the JD group was not correlated with the TG level in the liver. Furthermore, the significant difference in *Me* expression among the groups was not observed at 7 wk of age. At 7 wk of age, the expression level of *Srebp1 c*, encoding a transcriptional regulator of enzymes involved in fatty acid synthesis [33], was the lowest in offspring from the JD group, significantly lower than that in offspring from the HD group. The expression level of *G6 pdx*, involved in fatty acid synthesis [32], in offspring of the JD or HD group was significantly higher compared with offspring of the ND group. However, because *G6 pdx* is located upstream of *Fasn* [33] and *Acc* [33] regulated by *Srebp1 c*, fatty acid synthesis may have been suppressed by the decreased expression of *Srebp1 c* in the liver of JD group offspring. Therefore, the liver TG and visceral fat contents may have been decreased for these reasons.

The liver cholesterol level was significantly higher in offspring of the JD and HD groups than in those of the CD group at 18 d of age but was lower in the JD group than in the HD group. At 7 wk of age, the liver cholesterol level was significantly higher in the HD group than in the JD and CD groups. Because cholesterol metabolism in the liver was considered to be altered, the mRNA levels of genes involved in cholesterol synthesis and catabolism in the liver were measured. The expression of *Abcg5* involved in cholesterol efflux [34] was significantly lower in offspring of the JD group than in the HD group, and the expression levels of *Acat3* [35] and *Lxra* [36], related to cholesterol transport, were significantly lower in offspring of the HD and JD groups than in the CD group. Therefore, the transportation and secretion of cholesterol may have been suppressed in the liver of offspring from the JD group. For these reasons, the cholesterol content among the study diets was considered. Cholesterol in the Japanese diet was derived from animals, but it was not present in the control diet and was added to the high-fat diet (1.5 g/kg). The amount of cholesterol in the Japanese diet was approximately one-fifth that of the high-fat diet (0.3 g/kg). Therefore, the cholesterol level in the test diet may

have had an influence on cholesterol metabolism and levels in the liver of offspring.

Conclusion

Based on the results of this study, unlike a calorie-restricted diet, maternal consumption of the Japanese diet, even during pregnancy and lactation, does not adversely affect lipid metabolism in the offspring during infancy or later in life and does not increase the incidence of lifestyle-related diseases. Although further studies are required to determine exactly how maternal consumption of the Japanese diet during pregnancy and lactation affects offspring, this study confirmed no adverse effects on lipid metabolism. In our previous study in which mice were fed Japanese diets associated with different generations, a tendency of visceral fat accumulation was observed in those fed the modern Japanese diet group (2005 Japanese diet) compared with the control group (normal diet) [14,37]. However, in the present study, the amount of visceral fat was lower in offspring from the JD group than in the CD group, suggesting that maternal consumption of the Japanese diet during pregnancy and lactation had beneficial effects on offspring health. Therefore, some ingredients contained in the Japanese diet may be beneficial to fetal growth, but further studies are needed to clarify this.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.nut.2018.06.006.

References

[1] Ministry of Health, Labour and Welfare. Abridged life tables for Japan Available at: https://www.mhlw.go.jp/english/database/db-hw/lifetb16/index.html. Accessed December 1, 2016.

[2] Rains TM, Agarwal S, Maki KC. Antiobesity effects of green tea catechins: a mechanistic review. J Nutr Biochem 2011;22:1–7.

[3] Kim MH, Kang KS. Isoflavones as a smart curer for non-alcoholic fatty liver disease and pathological adiposity via ChREBP and Wnt signaling. Prev Med 2012;54(suppl):S57–63.

[4] Buckley JD, Howe PR. Long-chain omega-3 polyunsaturated fatty acids may be beneficial for reducing obesity—a review. Nutrients 2012;2:1212–30.

[5] Tsuduki T, Takeshika N, Nakamura Y, Nakagawa K, Igarashi M, Miyazawa T. DNA Microarray analysis of rat liver after ingestion of Japanese and American food. J Jpn Soc Nutr Food Sci 2008;61:255–64.

[6] Ashino NG, Saito KN, Souza FD, Nakutz FS, Roman EA, Velloso LA, et al. Maternal high-fat feeding through pregnancy and lactation predisposes mouse offspring to molecular insulin resistance and fatty liver. J Nutr Biochem 2012;23:341–8.

[7] Barker DJ, Osmond C. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000;108:545–53.

[8] Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. Environ Health 2012;11:42.

[9] García AP, Palou M, Sánchez J, Priego T, Palou A, Picó C. Moderate caloric restriction during gestation in rats alters adipose tissue sympathetic innervation and later adiposity in offspring. PLoS One 2011;6:E17313.

[10] Matveyenko AV, Singh I, Shin BC, Georgia S, Devaskar SU. Differential effects of prenatal and postnatal nutritional environment on β-cell mass development and turnover in male and female rats. Endocrinology 2010;151:5647–56.

[11] Akitake Y, Katsuraqi S, Hosokawa M, Mishima K, Ikeda T, Miyazato M, et al. Moderate maternal food restriction in mice impairs physical growth, behavior, and neurodevelopment of offspring. Nutr Res 2015;35:76–87.

[12] Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 2009;325:201–4.

[13] Larson-Meyer DE, Newcomer BR, Heilbronn LK, Volaufova J, Smith SR, Alfonso AJ, et al. Pennington CALERIE Team. Effect of 6-month calorie restriction and exercise on serum and liver lipids and markers of liver function. Obesity 2008;16:1355–62.

[14] Kitano Y, Honma T, Hatakeyama Y, Jibu Y, Kawakami Y, Tsuduki T, et al. Effects of historical differences in components of the Japanese diet on the risk of obesity in mice. J Jpn Soc Nutr Food Sci 2014;67:73–85.

[15] Hatakeyama Y, Kitano Y, Honma T, E S, Yamamoto K, Jibu Y, et al. Effects of Japanese food typical of that consumed during different periods in the past on breast milk-mediated lipid metabolism in offspring. J Jpn Soc Nutr Sci 2014;67:255–70.

[16] Ministry of Health, Labour and Welfare. Standard of Japanese meal intake 2010 (DAI-ICHI SHUPPAN) 62–117. Dietary Reference Intakes for Japanese-2010-. Available at: http://www.nibiohn.go.jp/en/files/Section_of_the_Dietary_Reference_Intakes/dris2010_eng.pdf#search=%27Dietary+Reference+Intakes+for+Japanese+%282010%29%27. Accessed August 2, 2017.

[17] The Ministry of Health, Labour, and Welfare's 2010 National Health and Nutrition Survey Report p62–63. National Institute of Health and Nutrition. Section of the National Health and Nutrition Survey. Available at: http://www.nibiohn.go.jp/eiken/english/research/project_nhns.html. Accessed August 2, 2017.

[18] Ministry of education culture sports science and technology. Standard Tables of Food Composition in Japan – 2015 - (Seventh Revised Edition). Available at: http://www.mext.go.jp/en/policy/science_technology/policy/title01/detail01/1374030.htm. Accessed August 2, 2018.

[19] Iwagaki Y, Sugawara S, Huruya Y, Sato M, Wu Q, E S, et al. The 1975 Japanese diet has a stress reduction effect in mice: search for physiological effects using metabolome analysis. Biosci Biotechnol Biochem 2018;82:709–15.

[20] Ishikawa H, Guo X, Sugawara S, Iwagaki Y, Yamamoto K, Tsuduki T. Effect of the Japanese diet during pregnancy and lactation or post-weaning on the risk of metabolic syndrome in offspring. Biosci Biotechnol Biochem 2018;82:515–24.

[21] Rouser G, Fleischer S, Yamamoto A. Two dimensional then layer chromatographic separation of polar lipids and determination of phospholipids by phosphorus analysis of spots. Lipids 1970;5:494–6.

[22] Mizowaki Y, Sugawara S, Yamamoto K, Sakamoto Y, Iwagaki Y, Kawakami Y, et al. Comparison of the effects of the 1975 Japanese diet and the modern Mediterranean diet on lipid metabolism in mice. J Oleo Sci 2017;66:507–19.

[23] Tsuduki T, Yamamoto K, E S, Hatakeyama Y, Sakamoto Y. High dietary fat intake during lactation promotes the development of social stress-induced obesity in the offspring of mice. Nutrients 2015;7:5916–32.

[24] Hoekstra M, Kruijt JK, Van Eck M, Van Berkel TJ. Specific gene expression of ATP-binding cassette transporters and nuclear hormone receptors in rat liver parenchymal, endothelial, and Kupffer cells. J Biol Chem 2003;278:25448–53.

[25] Ota M, Mori K, Nakashima A, Kaneko YS, Takahashi H, Ota A. Resistance to excessive body weight gain in risperidone-injected rats. Clin Exp Pharmacol Physiol 2005;32:279–87.

[26] Scott DK, Collier JJ, Doan TT, Bunnell AS, Daniels MC, Eckert DT, O'Doherty RM. A modest glucokinase overexpression in the liver promotes fed expression levels of glycolytic and lipogenic enzyme genes in the fasted state without altering SREBP-1 c expression. Mol Cell Biochem 2003;254:327–37.

[27] Field A. Discovering statistics using SPSS. 2nd ed London: Sage Publications; 2005.

[28] Ramírez-López MT, Vázquez M, Bindila L, Lomazzo E, Hofmann C, Blanco RN, et al. Maternal caloric restriction implemented during the preconceptional and pregnancy period alters hypothalamic and hippocampal endocannabinoid levels at birth and induces overweight and increased adiposity at adulthood in male rat offspring. Front Behav Neurosci 2016;10:208.

[29] Suzuki M, Shibanuma M, Kimura S. Effect of severe maternal dietary restriction on growth and intra-abdominal adipose tissue weights in offspring rats. J Nutr Sci Vitaminol 2010;56:293–8.

[30] Lukaszewski MA, Mayeur S, Fajardy I, Delahaye F, Dutriez-Casteloot I, Montel V, et al. Maternal prenatal undernutrition programs adipose tissue gene expression in adult male rat offspring under high-fat diet. Am J Physiol Endocrinol Metab 2011;301:E548–59.

[31] Palou M, Konieczna J, Torrens JM, Sánchez J, Priego T, Fernandes ML, et al. Impaired insulin and leptin sensitivity in the offspring of moderate caloric-restricted dams during gestation is early programmed. J Nutr Biochem 2012;23:1627–39.

[32] Kim J, Park J, Hong S, Kim MK. Effect of corn gluten and its hydrolysate consumptions on weight reduction in rats fed a high-fat diet. Nutr Res Pract 2009;3:200–7.

[33] Kim HJ, Takahashi M, Ezaki O. Fish oil feeding decreases mature sterol regulatory element-binding protein 1 (SREBP-1) by down-regulation of SREBP-1 c mRNA in mouse liver. A possible mechanism for down-regulation of lipogenic enzyme mRNAs. J Biol Chem 1999;274:25892–8.

[34] Dikkers A, de Boer JF, Groen AK, Tietge UJ. Hepatic ABCG5/G8 overexpression substantially increases biliary cholesterol secretion but does not impact in vivo macrophage-to-feces RCT. Atherosclerosis 2015;243:402–6.

[35] Toledo JD, Garda HA, Cabaleiro LV, Cuellar A, Pellon-Maison M, Gonzalez-Baro MR, et al. Apolipoprotein A-I Helsinki promotes intracellular acyl-CoA cholesterol acyltransferase (ACAT) protein accumulation. Mol Cell Biochem 2013;377:197–205.

[36] Martínez D, Pentinat T, Ribó S, Daviaud C, Bloks VW, Cebrià J, et al. In utero undernutrition in male mice programs liver lipid metabolism in the second-generation offspring involving altered Lxra DNA methylation. Cell Metab 2014;19:941–51.

[37] Honma T, Kitano Y, Kijima R, Jibu Y, Kawakami Y, Tsuduki T, et al. Comparison of the health benefits of different eras of Japanese Foods: lipid and carbohydrate metabolism focused research. Nippon Shokuhin Kagaku Kogaku Kaishi 2013;60:541–53.