表2. 外食頻度を5分位に分類した際の対象者特性 (n=3937) [a]

外食・中食の利用頻度(回/月)	1(最低値) (n=880) 8未満		2 (n=730) 9以上15以下		3 (n=788) 16以上23以下		4 (n=773) 24以上35以下		5(最高値) (n=766) 36以上	
年齢 (歳)	18.1 ± 0.4		18.1 ± 0.3		18.1 ± 0.3		18.1 ± 0.3		18.1 ± 0.3	
身長 (cm)	157.9 ± 5.5		157.9 ± 5.4		157.8 ± 5.2		157.8 ± 5.4		158.0 ± 5.2	
体重 (kg)	52.9 ± 8.2		52.2 ± 7.2		52.5 ± 7.7		52.0 ± 7.5		51.8 ± 7.6	
Body mass index (kg/m2)[b]	21.2 ± 3.0	*	20.9 ± 2.6		21.1 ± 2.9		20.8 ± 2.7		20.7 ± 2.7	
<18.5	13.4		15.5		13.5		14.7		15.8	
18.5-24.9	76.7		77.4		77.5		78.8		77.7	
>=25	9.9		7.1		9.0		6.5		6.5	
居住地										
北海道および東北	11.8		11.2		9.5		8.7		7.7	
関東	30.3		30.8		35.0		36.6		39.4	
北陸および東海	14.4		15.8		14.1		13.8		11.4	
近畿	17.3		20.1		19.3		21.6		21.1	
中国および四国	11.7		9.9		9.4		11.1		11.6	
九州	14.4		12.2		12.7		8.2		8.7	
居住地規模										
都市人口 100万人以上	17.6		18.9		20.6		20.3		22.3	
都市人口 100万人未満	65.3		65.9		64.8		63.5		64.6	
市町村	17.0		15.2		14.6		16.2		13.1	
喫煙習慣あり	1.0		0.8		1.0		0.9		3.7	
飲酒習慣あり	12.0		19.3		19.4		21.3		24.8	
総エネルギー(kcal/日)[b]	1676 ± 458	**	1711 ± 430	**	1786 ± 475	**	1844 ± 488	**	1991 ± 570	
脂質エネルギー比 (%)[b]	28.6 ± 6.0	**	29.6 ± 5.5	**	29.6 ± 5.7	**	30.5 ± 6.2		31.0 ± 6.0	
身体活動レベル	1.46 ± 0.13		1.46 ± 0.11		1.47 ± 0.13		1.47 ± 0.13		1.47 ± 0.11	
外食の利用頻度状況 (回/月)	4.5 ± 2.5		11.9 ± 1.9		19.3 ± 2.2		28.8 ± 3.4		52.8 ± 17.5	
ファーストフード頻度 (回/月)	0.9 ± 1.2		1.9 ± 1.9		2.3 ± 2.7		3.3 ± 3.6		6.2 ± 6.8	
レストラン・食堂頻度 (回/月)	1.7 ± 1.8		4.1 ± 3.1		7.1 ± 5.4		9.3 ± 6.8		14.3 ± 12.0	
コンビニエンスストア・売店頻度 (回/月)	1.4 ± 1.8		4.2 ± 3.1		7.0 ± 5.0		11.3 ± 7.4		22.7 ± 13.9	
コンビニ以外のデリカテッセン頻度 (回/月	0.5 ± 1.1		1.7 ± 2.4		2.8 ± 3.8		4.8 ± 6.0		9.5 ± 10.9	

a 平均値 ± 標準偏差。あるいは %。

b 最高位(5)に比べた平均値の差に関する有意差, *P < 0.05, **P < 0.001 (ダネットの t-検定).

表3. 栄養素等摂取量 (n =3937) [a]

外食・中食の利用頻度	1(最低値) (n=880) 8回未満/月		2 (n=730) 9回以上15回以下/月		3 (n=788) 16回以上23回以下/月		4 (n=773) 24回以上35回以下/月		5(最高値) (n=766) 36回以上/月	
エネルギー (kal/day)[b]	1676 ± 458	**	1711 ± 430	**	1786 ± 475	**	1844 ± 488	**	1991 ± 570	
脂質エネルギー (%)[b]	28.6 ± 6.0	**	29.6 ± 5.5	**	29.6 ± 5.7	**	30.5 ± 6.2		31.0 ± 6.0	
たんぱく質 (g/1000kcal)	33.1 ± 5.5		33.6 ± 5.4		33.4 ± 5.4		33.2 ± 5.2		33.1 ± 5.7	
炭水化物(g/1000kcal)	139.4 ± 17.4		138.9 ± 17.3		138.7 ± 17.0		138.5 ± 18.1		138.4 ± 17.8	
ナトリウム (mg/1000kcal)	2090.7 ± 561.8		2116.3 ± 541.0		2126.1 ± 558.5		2085.5 ± 558.8		2067.2 ± 539.3	
カリウム (mg/1000kcal)[b]	1067.6 ± 297.0		1095.6 ± 306.3	*	1089.6 ± 295.6	*	1067.8 ± 283.3		1051.9 ± 289.6	
カルシウム (mg/1000kcal)	256.5 ± 99.7		262.5 ± 99.9		259.6 ± 93.3		256.2 ± 94.2		261.0 ± 106.7	
マグネシウム(mg/1000kcal)[b]	116.6 ± 29.6		120.2 ± 30.9	**	119.6 ± 29.0	*	117.5 ± 29.2		114.8 ± 27.5	
リン (mg/1000kcal)	495.9 ± 101.2		506.3 ± 102.2		502.5 ± 100.2		497.9 ± 99.4		497.5 ± 107.3	
鉄 (mg/1000kcal)[b]	3.6 ± 0.9		3.7 ± 0.9	*	3.7 ± 0.9		3.6 ± 0.8		3.5 ± 0.9	
亜鉛 (mg/1000kcal)	4.0 ± 0.6		4.1 ± 0.6		4.1 ± 0.6		4.0 ± 0.6		4.1 ± 0.6	
銅 (mg/1000kcal)[b]	0.6 ± 0.1		0.6 ± 0.1	**	0.6 ± 0.1	*	0.6 ± 0.1		0.6 ± 0.1	
ビタミンA (μg/1000kcal)	258.5 ± 167.1		266.8 ± 197.8		257.5 ± 179.8		258.2 ± 142.2		257.3 ± 138.0	
レチノール(μg/1000kcal)	128.6 ± 133.6		131.9 ± 164.6		124.3 ± 139.7		129.7 ± 106.8		128.0 ± 102.1	
カロテン (μg/1000kcal)	1568.9 ± 1073.8		1629.2 ± 1055.7		1608.5 ± 1062.9		1551.7 ± 999.0		1561.9 ± 1057.6	
クリプトキサンチン(g/1000kcal)	127.4 ± 136.6		133.2 ± 150.5		132.1 ± 162.7		135.2 ± 159.4	*	116.4 ± 139.1	
ビタミン D (mg/1000kcal)	3.6 ± 2.1		3.7 ± 2.1		3.6 ± 2.0		3.5 ± 1.8		3.5 ± 2.2	
ビタミンB_1(mg/1000kcal)[b]	0.41 ± 0.10		0.42 ± 0.10	*	0.41 ± 0.09		0.41 ± 0.09		0.40 ± 0.09	
ビタミンB_2 (mg/1000kcal)	0.68 ± 0.20		0.70 ± 0.20		0.68 ± 0.19		0.68 ± 0.18		0.68 ± 0.20	
ナイアシン (mg/1000kcal)[b]	7.1 ± 2.2		7.2 ± 2.1	*	7.2 ± 2.1		7.1 ± 2.0		6.9 ± 2.0	
ビタミン C (mg/1000kcal)[b]	45.6 ± 22.7		46.0 ± 21.5	*	46.4 ± 23.6	*	45.4 ± 20.6		43.0 ± 19.9	
アルコール (g/1000kcal)	0.6 ± 2.4		0.6 ± 2.8		0.6 ± 3.5		0.5 ± 2.5		0.5 ± 1.9	
脂肪酸(g/1000kcal)	27.5 ± 6.0		27.5 ± 5.8		27.7 ± 5.7		27.9 ± 6.3		28.0 ± 6.0	
飽和脂肪酸 (g/1000kcal)	8.8 ± 2.4		8.8 ± 2.3		8.8 ± 2.2		8.9 ± 2.4		9.0 ± 2.5	
一価不飽和脂肪酸 (g/1000kcal)	11.1 ± 2.8		11.0 ± 2.7		11.1 ± 2.7		11.2 ± 2.9		11.2 ± 2.7	
多価不飽和脂肪酸 (g/1000kcal)	7.7 ± 1.8		7.7 ± 1.8		7.8 ± 1.8		7.8 ± 1.9		7.7 ± 1.8	
n-3系多価不飽和 (g/1000kcal)	1.4 ± 0.5		1.5 ± 0.4		1.5 ± 0.5		1.5 ± 0.5		1.4 ± 0.4	
n-6 系多価不飽和(g/1000kcal)	6.9 ± 1.6		6.9 ± 1.6		7.0 ± 1.6		7.0 ± 1.8		6.9 ± 1.6	
コレステロール(g/1000kcal)	162.7 ± 66.3		164.2 ± 62.1		162.1 ± 66.8		162.5 ± 62.3		166.0 ± 64.7	
水溶性食物繊維 (g/1000kcal)[1]	1.6 ± 0.6		1.7 ± 0.6	**	1.7 ± 0.6	**	1.6 ± 0.6		1.6 ± 0.5	
不溶性食物繊維(g/1000kcal)[b]	4.5 ± 1.4		4.6 ± 1.5	*	4.7 ± 1.5	*	4.5 ± 1.4		4.4 ± 1.4	
総食物繊維 (g/1000kcal)[b]	6.2 ± 2.0		6.4 ± 2.1	*	6.4 ± 2.0	*	6.2 ± 1.9		6.1 ± 1.9	

a 平均値 ± 標準偏差。あるいは %。

b 最高位(5)に比べた平均値の差に関する有意差, $*P < 0.05$, $**P < 0.001$ (ダネットの t-検定).

表4. 食品群摂取量 (n=3937) [a]

外食・中食の利用頻度(回/月)	1(最低値) (n=880) 8未満	2 (n=730) 9以上15以下	3 (n=788) 16以上23以下	4 (n=773) 24以上35以下	5(最高値) (n=766) 36以上
穀類 (g/1000kcal)	228.8 ± 70.4	227.1 ± 68.8	226.3 ± 67.5	224.7 ± 68.4	226.1 ± 68.7
種実類 (g/1000kcal)	0.6 ± 1.0	0.6 ± 1.3	0.6 ± 1.4	0.6 ± 1.4	0.6 ± 1.2
いも類(g/1000kcal)	15.6 ± 10.2	16.0 ± 11.3	16.3 ± 11.9	16.1 ± 11.7	15.3 ± 10.6
砂糖類(g/1000kcal)	5.9 ± 3.9	6.0 ± 3.4	6.2 ± 3.6	6.3 ± 3.7	6.0 ± 3.2
菓子類 (g/1000kcal)	33.3 ± 19.5	33.0 ± 17.8	32.9 ± 18.3	32.7 ± 17.0	33.3 ± 18.6
動物性脂肪 (g/1000kcal)	0.5 ± 0.8	0.5 ± 0.8	0.5 ± 0.8	0.5 ± 0.9	0.5 ± 1.0
植物性脂肪(g/1000kcal)	12.8 ± 6.6	12.5 ± 6.3	12.9 ± 6.5	12.9 ± 6.9	12.9 ± 6.7
豆・豆製品(g/1000kcal)	24.0 ± 17.9	25.8 ± 18.5	25.0 ± 17.2	24.6 ± 19.8	23.7 ± 17.3
果物 (g/1000kcal)	50.6 ± 48.2	50.3 ± 53.5	52.5 ± 57.7	51.8 ± 56.5	46.6 ± 45.7
緑黄色野菜 (g/1000kcal)	42.6 ± 34.6	44.2 ± 36.2	43.8 ± 36.5	41.7 ± 37.3	41.6 ± 32.8
その他の野菜 (g/1000kcal)[b]	57.5 ± 45.0	61.5 ± 50.4 *	60.3 ± 47.1	56.0 ± 46.0	54.7 ± 45.2
きのこ類 (g/1000kcal)	6.2 ± 8.6	6.6 ± 7.3	6.3 ± 6.8	6.1 ± 5.9	6.3 ± 8.4
藻類 (g/1000kcal)[b]	6.8 ± 8.2	8.0 ± 9.3 *	7.1 ± 8.5	6.7 ± 6.8	6.9 ± 8.0
調味料・香辛料 (g/1000kcal)	7.6 ± 4.1	7.7 ± 4.3	7.9 ± 4.7	7.7 ± 5.2	7.5 ± 4.1
アルコール飲料 (g/1000kcal)	7.3 ± 35.5	8.2 ± 45.1	7.0 ± 32.9	7.0 ± 36.2	5.7 ± 23.8
その他の飲み物 (g/1000kcal)	393.8 ± 283.9	393.1 ± 269.2	379.8 ± 273.9	394.6 ± 268.5	366.7 ± 252.9
魚類(g/1000kcal)	30.2 ± 18.5	31.0 ± 16.9	30.3 ± 19.1	30.4 ± 16.9	29.2 ± 17.6
肉類(g/1000kcal)	33.8 ± 17.0	33.9 ± 16.7	33.6 ± 16.6	34.0 ± 16.9	34.3 ± 17.5
卵類(g/1000kcal)	17.8 ± 14.2	18.3 ± 13.6	17.8 ± 14.4	17.6 ± 13.1	18.8 ± 14.1
乳・乳製品 (g/1000kcal)	81.7 ± 70.0	84.8 ± 71.0	84.4 ± 70.0	82.2 ± 67.8	89.0 ± 78.3

a 平均値 ± 標準偏差。あるいは %。

b 最高位(5)に比べた平均値の差に関する有意差, $*P < 0.05$, $**P < 0.001$ (ダネットの t-検定).

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Blood pressure change in a free-living population-based dietary modification study in Japan

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Objective **To assess whether dietary intervention in free-living healthy subjects is effective in improving blood pressure levels.**

Design **Open randomised, controlled trial.**

Setting **Free-living healthy subjects in two rural villages in north-eastern Japan.**

Participants **Five hundred and fifty healthy volunteers aged 40–69 years.**

Interventions **Tailored dietary education to encourage a decrease in sodium intake and an increase in the intake of vitamin C and carotene, and of fruit and vegetables.**

Main outcome measures **Blood pressure, dietary intake and urinary excretion of sodium, dietary carotene and vitamin C, and fruit and vegetable intake data were collected at 1 year after the start of the intervention.**

Results **During the first year, changes differed significantly between the intervention and control groups for dietary ($P = 0.002$) and urinary excretion ($P < 0.001$) of sodium and dietary vitamin C and carotene ($P = 0.003$). Systolic blood pressure decreased from 127.9 to 125.2 mmHg (2.7 mmHg decrease; 95% confidence interval, −4.6 to −0.8) in the intervention group, whereas it increased from 128.0 to 128.5 mmHg (0.5 increase; −1.3 to 2.3) in the control group. This change was statistically significant ($P = 0.007$). In contrast, the change in diastolic blood pressure did not significantly differ between the groups. In hypertensive subjects, a significant difference in systolic blood pressure reduction was seen between the groups ($P = 0.032$).**

Conclusion **Moderate-intensity dietary counseling in free-living healthy subjects achieved significant dietary changes, which resulted in a significant decrease in systolic blood pressure.** ***J Hypertens*** **24:451–458 © 2006 Lippincott Williams & Wilkins.**

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Keywords: blood pressure, dietary, fruit and vegetables, intervention studies, randomized controlled trials, sodium

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Introduction

Stroke is the most common cardiovascular disease in Japan [1]. Hypertension is the major cause of stroke, making the control of hypertension an important factor in the prevention of stroke. Non-pharmacological treatment is recommended as the first line of management for elevated blood pressure (BP) [2], primarily composed of lifestyle and diet modification. Evidence indicates that lifestyle measures such as weight reduction [3], moderation of alcohol consumption [4] and reduction in salt intake [5,6] are both feasible and effective in lowering BP. The importance of dietary factors was demonstrated in the DASH (Dietary Approach to Stop Hypertension) study, in which a diet rich in fruits and vegetables, and utilizing low-fat dairy products and products low in saturated and total fat, decreased systolic and diastolic BP compared with a diet representative of a typical diet for Americans [7].

Most clinical intervention trials targeted at the prevention and control of hypertension to date have been performed in academic study centers by expert personnel trained in the conduct of the trial. Because these studies were primarily designed to test the efficacy of their interventions, the intervention programs themselves were intensive. Due to the limited resources of the public health sector, however, broad implementation of such intensive lifestyle modification programs is difficult. Only a few lifestyle interventions have been performed in primary health care settings, and although most involved patients with hypertension, the interventions themselves were of low intensity and their effect was small.

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Moreover, these studies have frequently lacked evaluations of dietary compliance using validated measures.

The Hiraka Dietary Intervention Study [8] was a moderate-intensity, community-based randomized controlled trial designed to develop an effective dietary modification tool and system in an area with high mortality for stomach cancer and stroke. The dietary intervention was designed to decrease sodium (salt) and increase vitamin C and carotene intakes, with an emphasis on a decrease in salted foods and an increase in fruits and vegetables. The effects of the intervention were assessed not only using responses to a self-administered questionnaire but also the corresponding biomarkers. Here, we examine the effects of this dietary intervention on BP.

Methods

Study subject and design

The Hiraka Dietary Intervention Study was a community-based, randomized, cross-over trial held in 1998–2000 in two rural villages in Akita Prefecture, Japan.

Participants were recruited through public magazines and posters, in which potential respondents were asked to participate in a research project. Eligibility criteria for this study were: (1) age 40–69 years; and (2) physician permission to participate for those under medical treatment or dietary control. We expected to detect a difference in mean salt intake of 2.0 g/day (787 mg as sodium) or more between the intervention and control groups after 1 year, with a 5% alpha error (two-sided) and 20% beta error. A previous study reported a mean dietary sodium intake in a nearby area of 5940 mg/day (standard deviation ±2594) for men and 6013 mg/day (±2622) for women [9]. We estimated that a minimum of 352 participants would be needed for the trial, 176 allocated to each of the intervention and control groups. To allow for non-completion of the intervention study we aimed to recruit 470 participants. Five hundred and fifty volunteers (202 men and 348 women, aged 40–69 years) participated. All participants were informed of the study protocol, and written informed consent was obtained. They were assigned randomly into two groups and received tailored dietary education in either the first year (intervention group, $n = 274$) or the second year (control group, $n = 276$) by the same researcher. The random number of 0 (allocated to the first intervention group) or 1 (second intervention group) was generated for each subject using a function of Microsoft Excel. Subjects within one family were assigned to the same group. This procedure was repeated until the subject number in the two groups was the same.

Dietary goals at the group level were to reduce salt intake to less than 8 and 10 g/day in women and men, respectively, to increase carotene intake to more than 5000 μg/day, and to increase vitamin C intake to more than 200 mg/day. Our intervention consisted of individual 15-min dietary counseling sessions (two), a group lecture, and newsletters (two). First, dietary counseling was provided after the subject's annual health check-up. Individualized education schemes were prepared based on the results of the dietary survey and health check-up. About 5 months later, a second dietary assessment was performed and the same individual dietary counseling was provided to each subject. During the intervention period, a total of two newsletters about recommended diet were mailed to the participants to maintain motivation throughout the trial. The group lecture was performed at the mid-point of the intervention period.

To increase carotene and vitamin C intake, subjects were advised to increase their intake of fruit and vegetables. To decrease sodium intake, they were primarily instructed to decrease their intake of salted foods, such as miso (fermented and salted soybean paste), salted vegetable pickles, salted fish, and seasonings.

Data collection

A validated, self-administered diet history questionnaire (DHQ) was completed by all subjects three times, just before the annual health check-up conducted between April and August in 1998, 1999 and 2000. The DHQ surveyed dietary habits for the previous 1 month. The structure and validity of the DHQ have been described in detail elsewhere [10–12].

Forty-eight-hour urine samples were collected just after the annual health check-up. The subjects were requested to record the times at which they started and finished the urine collection. Urinary volume was measured, and a part of each sample was stored at −20°C until measurement. Whenever urine collection was missed, the estimated volume was reported by the subject and added to that of the collected urine to estimate the total urinary volume. The urinary concentrations of sodium and potassium were analyzed by flame photometry and creatinine by Jaffe's procedure using an autoanalyzer (Hitachi Clinical Analyzer 7070; Tokyo, Japan). The expected intakes were computed using observed urinary excretion, as reported in a carefully designed balance study, namely 0.86 for sodium and 0.77 for potassium [13].

BP was measured at the annual health check-up by trained nurses, using a sphygmomanometer OKOSE-300 model (Matsuyoshi & Co., Tokyo, Japan) according to a common protocol. A single measurement was performed in this trial. All measurements at each point were conducted by one nurse who was engaged in the health check-ups, and not by study staff. The nurse was blinded to the intervention assignment and was requested by the study staff not to inquire about the subject's allocation at BP measurement.

Subjects were asked to sit calmly and without talking for at least 2 min before measurement, with their legs uncrossed and their arms crossed at heart level.

Medical history, smoking status and anthropometric data were also collected at the annual health check-up. Classification as hypertensive or normotensive was based on the results of the health check-up. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Outcomes and statistical analysis

The effects of dietary intervention were examined using data from the first half of the study; that is, the group receiving dietary intervention in the first year as the intervention group. Because follow-up study after termination of the intervention suggested that the effects of intervention on diet were maintained well over 4 years, the decision was made to simplify assessment by excluding the data from the second half of the study. Subjects were excluded from the analysis of dietary data if they met either of the following criteria: (1) the DHQ was incomplete for either the pre- (baseline) or post-intervention (year 1); and (2) estimated energy intake was less than 50% of the energy requirement for a sedentary lifestyle or greater than 150% of that for a vigorous lifestyle.

Primary study outcome was the effect of intervention during the first year, namely the difference in changes between the intervention and control groups. Mean daily intakes of energy, targeted nutrients and mean urinary sodium at baseline and year 1 were calculated, with values at each point for fruits and vegetables, as well as alcohol, carotene, and vitamin C, transformed by the natural logarithm before calculation, to account for the skewing of distribution to the right. Mean values of variables for the groups at baseline were compared by the *t*-test. Proportions at baseline were tested by the χ^2 test. Differences from baseline to year 1 within groups are presented with 95% confidence intervals (95% CI). Analyses of covariance (ANCOVA) were conducted to investigate differences in outcome measure at year 1 between the randomized groups. Baseline values of each variable were included as covariates. For BP analysis, baseline BP and change in alcohol intake and body weight were included as covariates. All analyses were done with SAS statistical software (SAS Institute Inc., Cary, North Carolina, USA, version 8.0).

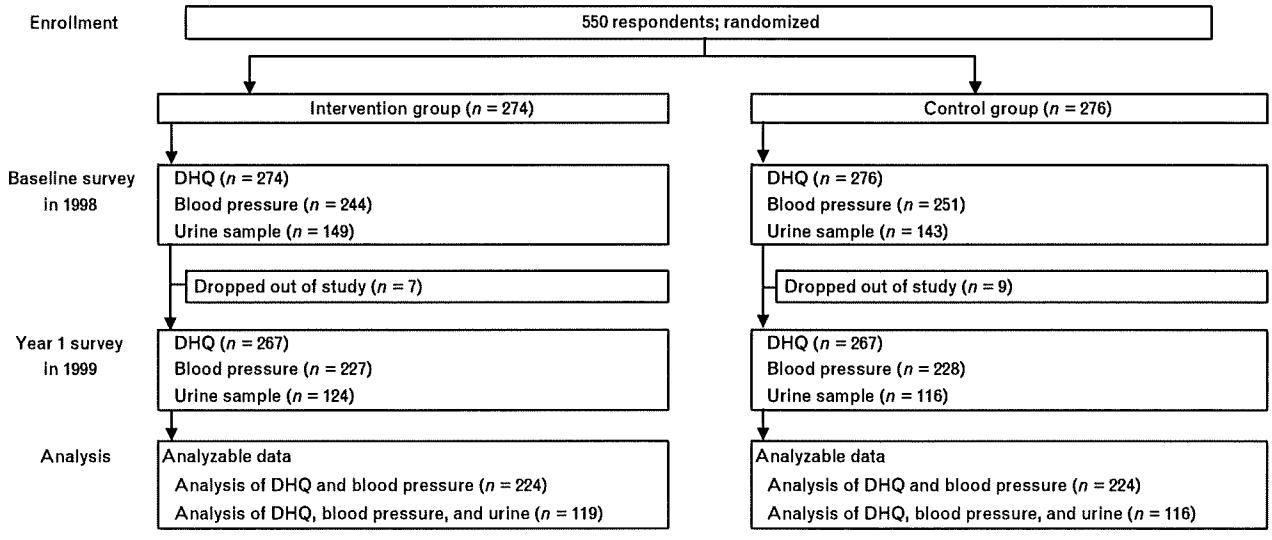
Results

Baseline characteristics

A total of 292 urine samples were obtained from 550 respondents who completed the DHQ at baseline (Fig. 1), and 240 samples from 534 subjects who completed the DHQ at year 1. Analysis included 235 and 448 subjects with and without urinary data, respectively.

Table 1 shows baseline variables for the intervention and control groups. Mean age of participants was 56.4 years. Mean systolic BP (SBP) and diastolic BP (DBP) did not statistically differ between the groups. Among participants, 11% (26 and 23 subjects in the intervention and control group, respectively) were receiving antihypertensive drug treatment at the beginning of the trial. Antihypertensive medication status of these subjects

Fig. 1



Number of study subjects. DHQ, diet history questionnaire.

Table 1 Subject characteristics at baseline

	Intervention group ($n = 224$)	Control group ($n = 224$)	P^a
Age (years)[b]	56.3 (41.2, 71.4)	56.4 (40.5, 72.4)	0.863
Sex (% female)	68.3	67.0	0.762
Body height (cm)[b]	154.9 (140.6, 169.2)	155.2 (139.1, 171.4)	0.978
Body weight (kg)[b]	56.7 (39.5, 73.8)	56.0 (39.1, 72.9)	0.996
Body mass index (kg/m^2)[b]	23.6 (17.9, 29.3)	23.2 (17.6, 28.8)	0.949
Blood pressure (mmHg)[b]			
Systolic blood pressure	127.9 (93.2, 162.5)	128.0 (97.4, 158.5)	0.955
Diastolic blood pressure	75.9 (53.9, 97.8)	76.3 (55.9, 96.6)	0.720
Alcohol drinker (%)	38.8	40.2	0.772
Hypertension (%)	23.7	24.1	0.912
On antihypertensives (%)	11.6	10.3	0.650
Diabetes (%)	3.6	3.1	0.793
Hyperlipidemia (%)	5.8	10.3	0.082

[a]P value for comparison between groups. [b]Values are mean and 95% confidence intervals.

did not change throughout the trial (data not shown). There were no statistically significant differences between the groups in age and sex distribution or other baseline variables.

Effect of intervention on lifestyle factors and dietary variables

Mean body weight and lifestyle factors and their changes from baseline to year 1 are presented in Table 2. No statistically significant change was observed between the groups. Daily intake of energy and nutrients and their changes are also presented in Table 2. At year 1, intake of fruit and vegetables and of dietary carotene and vitamin C increased significantly more in the intervention group ($P < 0.05$). Sodium intake in the intervention group decreased by 15 mmol/day (95% CI: −26, −4), but increased by 11 mmol/day (−0, +22) in the control group. This difference in change between the two groups was statistically significant ($P = 0.002$). Mean urinary excretion of sodium and potassium and the corresponding daily intake are shown in Table 3. Excretion and intake of sodium in the intervention group decreased by 49 (95% CI: −62, −36) and 11 mmol/day (−25, +4), respectively. This difference in change between the two groups was statistically significant ($P < 0.001$).

Effects of intervention on BP

Table 4 shows that SBP in the intervention group decreased from 127.9 to 125.2 mmHg (−2.7 mmHg change; 95% CI: −4.6, −0.8), but in the control group increased from 128.0 to 128.5 mmHg (+0.5 mmHg change; −1.3, +2.3), with this difference in change between the groups being statistically significant ($P < 0.01$). DBP changed from 75.9 to 74.8 mmHg (−1.0 mmHg change; 95% CI: −2.4, +0.3) in the intervention and from 76.3 to 75.9 mmHg (−0.3 mmHg change; −1.7, +1.1) in the control group. This difference in change between the groups was not statistically significant.

Data for the subgroup of subjects from whom urine was collected were analyzed separately. Results showed no difference in baseline SBP and DBP between those with and without urine collection (data not shown). SBP changed for urine collectors by −3.0 mmHg (95% CI: −5.7, −0.2) in the intervention group, whereas it changed by +0.3 mmHg (−2.5, +3.1) in the control group. This difference in change between the groups being statistically significant ($P < 0.05$).

BP data were also analyzed by hypertensive status. In the hypertensive subjects, SBP changed by −5.6 mmHg (95% CI: −9.3, −2.0) in the intervention group, whereas it changed by +1.4 mmHg (95% CI: −3.6, 6.3) in the control group. This difference in change between the groups was statistically significant ($P < 0.05$). In normotensive subjects, the decrease in SBP was also greater in the intervention group compared to the control group, but this difference in change did not reach the level of statistical significance ($P = 0.075$). Further, no statistically significant changes in DBP were observed between the two groups in either subgroup analysis.

Discussion

This 1-year dietary, moderate-intensity, community-based intervention trial demonstrated a significant decrease in SBP level. A greater decrease in average dietary intake and urinary excretion of sodium was seen in the intervention group than in the control group. An increase in fruit and vegetable intake was accompanied by an increase in carotene and vitamin C intake.

Several community-based, large-scale, randomized trials on the effects of dietary intervention on BP have been reported to date. However, the variability of lifestyle intervention topics and their intensity makes it difficult to compare the BP changes achieved. Further, most of these previous studies targeted only hypertensive subjects.

Changes in BP and urinary sodium

Brunner *et al.* [14] performed a meta-analysis of randomized controlled trials designed to investigate the primary prevention of chronic diseases, and evaluated the effects

Table 2 **Body weight and nutrient and food intakes at each point**

	Intervention group ($n = 224$)			Control group (n = 224)				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[c] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[c] (95% CI)	Adjusted between-group difference in change[d] (95% CI)	Adjusted *P* value[e]
Body weight (kg)	56.7 (39.5, 73.8)	56.5 (39.4, 73.7)	−0.1 (−0.3, 0.1)	56.0 (39.1, 72.9)	55.9 (39.2, 72.7)	−0.1 (−0.4, 0.1)	0.0 (−0.3, 0.3)	0.907
Moderate physical activity[a] no. (%)	223 (99.6%)	223 (99.6%)	0 (0%)	224 (100%)	224 (100%)	0 (0%)	0 (0%)	–
Current smoker[a] no. (%)	22 (9.8%)	22 (9.8%)	0 (0%)	26 (11.6%)	26 (11.6%)	0 (0%)	0 (0%)	–
Energy intake (MJ/day)	8.56 (3.43, 13.68)	8.44 (3.46, 13.41)	−0.12 (−0.38, 0.15)	8.15 (3.36, 12.96)	8.30 (3.40, 13.20)	0.16 (−0.13, 0.44)	−0.13 (−0.49, 0.22)	0.454
Alcohol (g/day)	3.5[b] (−1.6, 76.4)	3.0[b] (−1.6, 57.7)	−2.9 (−4.7, −1.2)	3.6[b] (−1.6, 76.2)	3.2[b] (−1.6, 65.7)	−1.6 (−3.7, 0.5)	−1.3 (−3.6, 1.0)	0.270
Nutrient intake								
Carotene (μg/day)	2159[b] (507, 9196)	2622[b] (677, 10156)	468 (166, 771)	1789[b] (331, 9676)	1944[b] (377, 10036)	170 (−77, 418)	521 (184, 858)	0.003
Vitamin C (mg/day)	107[b] (32, 358)	123[b] (42, 362)	15 (3, 26)	95[b] (24, 376)	100[b] (27, 364)	1 (−9, 12)	19 (6, 31)	0.003
Sodium (mmol/day)	237 (76, 397)	222 (54, 390)	−15 (−26, −4)	229 (64, 395)	240 (61, 420)	11 (−0, 22)	−23 (−37, −8)	0.002
Potassium (mmol/day)	71 (18, 123)	73 (18, 128)	2 (−1, 6)	65 (17, 113)	66 (20, 113)	1 (−2, 4)	4 (−1, 8)	0.081
Dietary fiber (g/day)	15.6 (3.1, 28.0)	16.2 (4.1, 28.3)	0.6 (−0.2, 1.5)	14.3 (3.2, 25.4)	14.6 (4.2, 25.1)	0.3 (−0.4, 1.0)	1.0 (0.0, 1.9)	0.040
Calcium (mg/day)	691 (59, 1323)	690 (106, 1274)	−1 (−45, 43)	621 (129, 1113)	663 (83, 1244)	42 (6, 78)	−7 (−56, 43)	0.792
Food intake								
Vegetables (g/day)	252.8[b] (72.2, 879.3)	269.3[b] (85.0, 848.1)	15.1 (−12.8, 42.9)	226.4[b] (62.4, 815.2)	227.3[b] (65.7, 781.0)	−2.1 (−19.7, 15.5)	34.2 (5.3, 63.0)	0.020
Fruits (g/day)	63.3[b] (7.5, 486.9)	84.5[b] (12.4, 543.0)	24.3 (11.5, 37.1)	59.3[b] (6.2, 503.5)	63.1[b] (6.8, 523.8)	2.0 (−10.0, 13.9)	23.1 (7.9, 38.4)	0.003

[a]Number and percentage of subjects. [b]Mean values at each point were transformed by the natural logarithm before computation because of the skewed distributions. They were back-transformed to show means and 95% confidence intervals (CIs). [c]Difference between baseline and year 1. [d]Difference between intervention group and control group in change after adjustment for baseline intake. [e]*P* values for comparison of mean at year 1 between the intervention group and control group by ANCOVA after adjustment for baseline intake.

Table 3 **Dietary intake and 48-h urinary excretion of sodium and potassium [means and 95% confidence intervals (CIs)] among subjects who completed urine collection at two points**

	Intervention group ($n = 119$)			Control group ($n = 116$)				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[b] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[b] (95% CI)	Adjusted between-group difference in change[c] (95% CI)	Adjusted *P* value[d]
Sodium (mmol/day)								
Dietary intake	242 (85, 398)	229 (65, 393)	−13 (−29, 3)	235 (78, 392)	247 (65, 428)	12 (−5, 28)	−21 (−41, −1)	0.040
Urinary excretion[a]	248 (103, 393)	199 (62, 335)	−49 (−62, −36)	248 (94, 402)	237 (50, 424)	−11 (−25, 4)	−39 (−56, −21)	<0.001
Potassium (mmol/day)								
Dietary intake	73 (22, 123)	75 (25, 125)	2 (−3, 7)	69 (20, 117)	69 (22, 117)	1 (−4, 5)	4 (−2, 9)	0.204
Urinary excretion[a]	66 (26, 107)	59 (18, 100)	−7 (−11, −3)	66 (27, 105)	61 (17, 105)	−4 (−8, −1)	−2 (−7, 3)	0.408

[a]Expected intake was considered to be observed urinary excretion divided by 0.86 for sodium and 0.77 for potassium. See text for details. [b]Difference between baseline and year 1. [c]Difference between intervention group and control group in change after adjustment for baseline value. [d]*P* values for comparison of mean at year1 between the intervention group and control group by ANCOVA after adjustment for baseline value.

Table 4 Blood pressure [mean and 95% confidence interval (CI)] at two points

	Intervention group			Control group				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[a] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[a] (95% CI)	Adjusted between-group difference in change[b] (95% CI)	Adjusted P value[c]
All subjects	($n = 224$)			($n = 224$)				
SBP (mmHg)	127.9 (93.2, 162.5)	125.2 (93.7, 156.7)	−2.7 (−4.6, −0.8)	128.0 (97.4, 158.5)	128.5 (99.0, 158.0)	0.5 (−1.3, 2.3)	−3.1 (−5.4, −0.9)	0.007
DBP (mmHg)	75.9 (53.9, 97.8)	74.8 (53.3, 96.4)	−1.0 (−2.4, 0.3)	76.3 (55.9, 96.6)	75.9 (55.9, 95.9)	−0.3 (−1.7, 1.1)	−0.9 (−2.6, 0.8)	0.307
Urine collection	($n = 119$)			($n = 116$)				
SBP (mmHg)	128.0 (91.6, 164.3)	125.0 (92.9, 157.2)	−3.0 (−5.7, −0.2)	128.4 (98.6, 158.2)	128.7 (98.1, 159.3)	0.3 (−2.5, 3.1)	−3.4 (−6.8, −0.0)	0.048
DBP (mmHg)	75.8 (53.5, 98.2)	74.5 (53.8, 95.2)	−1.3 (−3.1, 0.4)	76.8 (57.6, 96.1)	75.8 (56.5, 95.0)	−1.1 (−3.0, 0.9)	−0.8 (−3.0, 1.5)	0.502
Normotensive	($n = 171$)			($n = 170$)				
SBP (mmHg)	123.3 (91.2, 155.4)	121.6 (91.8, 151.3)	−1.8 (−4.0, 0.4)	124.1 (98.2, 150.0)	124.3 (98.3, 150.3)	0.2 (−1.6, 2.1)	−2.3 (−4.7, 0.2)	0.075
DBP (mmHg)	73.6 (52.6, 94.5)	72.5 (52.6, 92.5)	−1.1 (−2.7, 0.5)	74.7 (55.6, 93.8)	74.2 (54.8, 93.6)	−0.5 (−2.1, 1.1)	−1.2 (−3.1, 0.7)	0.233
Hypertensive	($n = 53$)			($n = 54$)				
SBP (mmHg)	142.5 (116.2, 168.8)	136.9 (111.4, 162.3)	−5.6 (−9.3, −2.0)	140.2 (108.4, 172.0)	141.6 (116.6, 166.5)	1.4 (−3.6, 6.3)	−5.2 (−9.9, −0.4)	0.032
DBP (mmHg)	83.3 (64.5, 102.0)	82.4 (62.5, 102.3)	−0.9 (−3.3, 1.5)	81.1 (59.9, 102.3)	81.3 (63.0, 99.6)	0.2 (−2.9, 3.3)	0.1 (−3.3, 3.4)	0.971

[a]Difference between baseline and year 1. [b]Difference between intervention group and control group in change after adjustment for baseline values and change in alcohol intake and body weight. [c]P values for comparison of mean at year 1 between the intervention group and control group by ANCOVA after adjustment for baseline values and changes in alcohol intake and body weight. SBP, systolic blood pressure; DBP, diastolic blood pressure.

of dietary change on BP in free-living subjects. This meta-analysis included relatively intensive dietary interventions such as monthly group sessions and several individual counseling sessions. Among the four studies which aimed to reduce sodium intake, overall mean net urinary sodium reduction was 32 mmol/24 h. Further, the mean net BP changes over 9–18 months were −1.9 mmHg (95% CI: −3.0, −0.8) for SBP and −1.2 mmHg (−2.6, 0.2) for DBP. The net changes in BP and urinary sodium excretion seen in the present study were slightly greater than the results of this meta-analysis.

Change in BP among hypertensive subjects

Analysis of subjects by hypertensive status showed that the effect of dietary modification on BP was greater in subjects of the hypertensive subgroup. The most recent meta-analysis of clinical trials of salt reduction [15] showed a 4.96/2.73 mmHg decrease in hypertensives ($P < 0.001$ for both SBP and DBP). The effect on SBP in the present hypertensive subjects was comparable with these previous results. Dietary modification might prevent or delay the initiation of medication in hypertensive subjects with BP levels that straddle the threshold for antihypertensive medication.

Changes in BP and intake of other nutrients and lifestyle factors

The present study focused on the increase in the intake of vitamin C and carotene by recommendation of more fruits and vegetables. Results showed a moderate increase in carotene, vitamin C and dietary fiber intake, but not in potassium or calcium. Previous observational studies have reported significant inverse associations between BP and the intake of vitamin C, dietary fiber, potassium, magnesium and calcium [16–19]. The effectiveness of these nutrients has also been confirmed in clinical trials of dietary fiber, potassium, magnesium and calcium [20–23]. Furthermore, lifestyle factors such as physical activity, weight loss, alcohol consumption and smoking also influence BP level [24–26]. We did not observe changes in these variables. The decrease in BP seen in the present study might be attributable at least to some extent to increases in the intake of vitamin C and dietary fiber.

Changes in BP and fruit and vegetable intake

The present study focused on the use of fruits and vegetables to increase carotene and vitamin C intake.

Several previous clinical studies have examined the effect of dietary intervention on BP. The DASH trial, a well-controlled, randomized, clinical trial [7] to assess the effects of dietary patterns on BP, showed a decrease in SBP of 2.8 mmHg and in DBP by 1.1 mmHg by an increase in dietary fruit and vegetable intake for 8 weeks. In a subsequent study [27], this hypotensive effect of the

DASH diet was enhanced by its combination with a reduced sodium diet (100 and 50 mmol/day). The results of the present study support those of the DASH trials by showing similar, albeit somewhat weaker, results in a free-living, general population.

Further, Nowson *et al.* [28] conducted a cross-over dietary intervention study using a community-living subject. They reported a significant decrease in BP by a low-sodium, high-potassium diet and a DASH-type diet (DASH diet with moderate sodium reduction). The tendency of the results was similar to those of the present study, but the size of the effect was greater. However, the study population in their study was smaller ($n = 94$), the study period shorter (4 weeks), and the intervention more intensive (bi-weekly contact) than in the present study. Salt-free bread, salt-free margarine or both were provided to the intervention subjects. In contrast, no food was provided in the present study. The method used in the present study appears to be more practicable for use in community settings than that in the study of Nowson *et al.* [28].

Study limitations

Because this study was an open trial, the possibility of interaction between the intervention and control groups, such as information exchange, cannot be ruled out. In the control group, however, no statistically significant change in targeted nutrients and foods between the baseline and year 1 points was observed, suggesting that any interaction between the groups may have been negligible. Nevertheless, the possibility of some general information exchange remains, and the results should therefore be interpreted with caution.

To examine a practical model for population-based lifestyle improvement intervention, our present intervention study was performed in a primary health care setting rather than an academic center setting. Measurement of BP was conducted at the annual health check-up as a routine component of that check-up, and thus only a single measurement was done instead of multiple measurement. Nevertheless, conditions between the two groups were the same.

Because they had been previously exposed to various public health campaigns in the study area on the importance of decreasing salt intake, the present study subjects were relatively well-motivated to reduce their salt intake [29]. Moreover, they were provided further information about the unfavorable effect of dietary sodium on health prior to the start of the study. We therefore presume that they were more receptive to the message to decrease sodium given in this study. The decrease in sodium and consequent decrease in BP observed in this trial indicates the effectiveness of this intervention method for motivated persons. Further studies are necessary to determine whether this intervention method is equally effective on dietary and BP modification in other populations.

In conclusion, these findings indicate that the effects of dietary interventions undertaken to reduce the intake of sodium and increase that of fruit and vegetables may be expected to decrease BP level in free-living populations. The present randomized, controlled trial involved a relatively large number of free-living subjects and examined the change in dietary habits and BP over 1 year. The intervention method used here may represent an efficient and practicable model for population-based BP improvement in common primary care settings.

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Histidine Intake May Negatively Correlate with Energy Intake in Human: A Cross-Sectional Study in Japanese Female Students Aged 18 Years

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Summary L-Histidine (histidine), a precursor of neuronal histamine, has recently been hypothesized to suppress food intake. The association between dietary histidine and energy intake was examined among 1,689 Japanese female students of dietetic courses aged 18 y. Nutrient intakes were assessed over a 1-mo period with a validated, self-administered, diet history questionnaire. Both intake of histidine and the ratio of histidine to protein (histidine/protein) statistically and positively correlated with energy intake. After adjustment for potential non-dietary confounding factors, including body height, body weight, physical activity level, and rate of eating, both the histidine intake and histidine/protein ratio statistically and positively correlated with energy intake (Pearson's correlation coefficient, r=0.62 and 0.12, respectively, p<0.001). Moreover, when protein or protein excluding histidine was additionally included into the covariates in order to minimize the effect of dietary factors and other amino acids, both histidine intake and histidine/protein ratio turned out to show a statistically negative correlation with energy intake (r=−0.22 and −0.23, respectively, p<0.001). Considering the influence of unavoidable various covariates, we found an inverse association between histidine/protein ratio and energy intake among the young female Japanese students.

Key Words dietary histidine, energy intake, young Japanese women, epidemiology

Hypothalamus neuronal histamine has been shown to regulate food intake through the histamine H_1-receptor in the ventromedial hypothalamic nucleus and the paraventricular nucleus (*1–3*). Recently, it has been hypothesized that L-histidine (histidine), an essential amino acid, might also control food intake through its conversion into histamine (*4–6*). Histidine preloads delivered by intraperitoneal injection (IP) into rats reduced food intake (*7, 8*) and increased water intake (*8, 9*). Although histidine given by the intragastric route showed a low sensitivity to food intake suppression compared to IP, dietary histidine might also play a role in regulating food intake in the short-term, at least partially through the histaminergic pathway (*8*). However, its physiological importance has not been established.

On the other hand, in human studies, the effect of histidine on food intake was examined in respect to the alterations in zinc metabolism accompanied by anorexia in the 1970s (*10–13*). Administration of a large dose of histidine induced zinc deficiency, which led to functional losses of taste, smell, appetite, and food intake. Therefore, according to the previous points of view from human studies, feeding suppression has seemed to be caused by alteration of zinc metabolism rather than direct effects of histidine. However, pretreatment with alpha-fluoromethyl histidine (FMH), a specific suicide inhibitor of histamine-synthesizing histidine decarboxylase (HDC), attenuated histidine-induced feeding suppression in animal studies (*5, 6*). These results support the view that histidine-induced histamine rather than the histidine-induced zinc deficiency affects food intake. Although the available evidence in animal studies strongly suggests the effect of histidine on food intake, in human, only two small observational studies conducted in Japan examined this issue (*14, 15*).

To examine the association in more detail, we conducted a cross-sectional study using a large and homogenous sample consisting of 1,689 Japanese female dietetic students aged 18 y.

SUBJECTS AND METHODS

Subjects. The subjects were freshmen who entered dietetic courses at 22 colleges and technical schools in Japan in April 1997 (n=2,069). All the questionnaires were distributed between April 7 and 21, 1997. A total of 2,063 students (2,017 women and 46 men) returned the completed questionnaires within 1 wk (response rate, 99.7%). Faculty members of each school checked the submitted questionnaires. When missing replies and/or errors were found, the subjects were requested to answer the questions again. All question-

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naires were checked at least once by the local staff and once by the staff of the study center. The entire survey was completed before the end of May.

Assessment of dietary habits. We used a self-administered diet history questionnaire (DHQ). The DHQ is a validated 16-page questionnaire assessing dietary habits in the previous 1 mo. Intakes of 147 food items, 16 nutrients, and total energy intake were calculated using an ad-hoc computer algorithm developed to analyze the questionnaire. The 147 foods from the DHQ were grouped into 17 food groups, mainly according to the food composition tables of Japanese foods, 5th revised edition (*16*). The DHQ has been validated by comparison to 3-d dietary records. The Pearson's correlation coefficients were 0.48–0.55 for the macronutrients used in the study and 0.48 for energy. Moreover, the mean reported intakes of energy and three macronutrients assessed by the DHQ were close to the reported intakes assessed by dietary records, i.e., within a ±3% difference. A more detailed description of the questionnaire, the methods of calculating nutrients, and the validity are given elsewhere (*17, 18*). We estimated histidine intake using the DHQ attached with the amino acid food composition table (*19*) and supplemental food composition table of amino acid proposed by Todoriki et al. (*20*). We examined the validity of histidine intake from the DHQ by comparison with 16-d dietary records (16-d DRs) among Japanese men (n=92) and women (n=92) aged 30–78 y. The mean intake assessed by the DHQ was 2,192±774 mg/d for men and 2,144±628 mg/d for women. The mean intake assessed by 16-d DRs was 2,084±492 mg/d and 1,744±326 mg/d, respectively. Moreover, the Pearson's correlation coefficients were 0.37 and 0.32 for men and women, respectively.

Assessment of lifestyle variables. Lifestyle variables were obtained from the 4-page questionnaire designed for this survey. It included the frequency of sports club activity and smoking habits. The physical activity level was assessed by the monthly frequency of sports club activity without inquiring into the types of sports, their intensity or duration. The subjects who engaged in sports club activity at least once per week in the previous month were defined as 'physically active' and the others as 'sedentary.' Smoking habits were divided into three categories: never-, past-, and current smokers. Current smokers were defined as subjects who reported smoking cigarettes on a regular basis, whereas past-smokers were defined as subjects who quit smoking. Data on birthday, self-reported body weight, height, and rate of eating were obtained from the DHQ. Rate of eating was self-reported according to one of five qualitative categories: 'very slow,' 'relatively slow,' 'medium,' 'relatively fast,' and 'very fast.' The validity of this rating was described in the previous paper (*21*). BMI was calculated as body weight (kg) divided by the square of body height (m^2).

Statistical analysis. We included 1,689 subjects (83.3%) who satisfied the following two criteria in the analysis:

1) Women aged 18 y on the surveyed day (n=1,744);

2) Those with reported energy intake of more than or equal to half of the energy requirement of the lowest physical activity category and less than 1.5 times the energy requirement of the highest physical activity category (*22*), i.e., the subjects with reported energy intake of 3.0–14.4 MJ/d (n=1,980).

Macronutrient intakes were energy-adjusted using an energy density model, i.e., the percentage of energy intake (%E). Histidine was divided by the protein intake, i.e., histidine/protein (mg/g).

Differences in the means of energy intake between categories were tested by the Student's t test or ANOVA. Multiple regression analysis was performed to examine the effect of daily histidine intake on energy intake. Several confounding factors have been reported for energy intake, such as body height, body weight, physical activity level, and rate of eating (*21, 23–25*). In this analysis, these non-dietary variables were included in the models as covariates (Model 2). Furthermore, we additionally adjusted for dietary variables such as dietary fiber and protein as dietary confounding factors (Model 3). When histidine intake was used as an independent variable, protein excluding histidine (protein−histidine) was included as a dietary covariate to adjust for possible effects of other types of amino acids. We also computed the partial correlation coefficients between each independent variable and energy intake adjusting for other independent variables.

All statistical analyses were performed using version 8.2 of the SAS software package (SAS Institute, Inc., Cary, North Carolina, USA). A p-value of <0.05 was considered significant.

RESULTS

Table 1 shows the characteristics of the subjects and Pearson's correlation coefficients for each variable with energy intake. The mean BMI±SD for the subjects was 20.8±2.6 kg/m^2, and 95% of the subjects were classified into the non-obese group (25 kg/m^2 < BMI). In Pearson's correlation coefficient, a significant correlation with energy intake was observed for body height (p<0.001), sports club activity (p=0.04), and all nutrients described in Table 1, such as macronutrients, total dietary fiber, histidine, protein extracting histidine, and histidine/protein ratio (p<0.001 in all nutrients). As for categorical variables, the mean energy intake was significantly different between the two physical activity levels (p<0.001) and among the five categories of rate of eating (p<0.001).

Table 2 shows the results of multiple regression analysis with energy intake as a dependent variable. Histidine positively correlated with energy intake regardless of the adjustment of non-dietary factors (partial regression coefficient, β=0.002 in Model 1: β=0.002 in Model 2). However, after additional adjustment for dietary factors, such as total dietary fiber and protein excluding histidine, histidine intake turned out to show a negative correlation with energy intake (β=

Table 1. Physiological characteristics, lifestyle variables, and nutrient intakes of the subjects[a], and Pearson's correlation coefficients with energy intake.[b]

	Mean±SD (n=1,689)	Pearson's correlation coefficient with energy intake	p-value	t-value[e]	p-value
Body height (cm)	158.0±5.2	0.13	<0.001	—	—
Body weight (kg)	51.8±7.3	0.03	0.22	—	—
Body mass index (kg/m^2)	20.8±2.6	−0.03	0.17	—	—
Sports club activity (d/mo)	1.7±4.2	0.05[c]	0.04	—	—
Nutrient intake					
Energy intake (MJ/d)	7.2±2.0	—	—	—	—
Carbohydrate (g/d)	234.1±58.8	0.86	<0.001	—	—
Fat (g/d)	58.0±24.1	0.88	<0.001	—	—
Total protein (g/d)	63.3±21.0	0.86	<0.001	—	—
Total dietary fiber (g/d)	12.0±4.7	0.66	<0.001	—	—
Histidine (mg/d)	2081±785	0.79	<0.001	—	—
Protein excluding histidine (g/d)	61.2±20.3	0.86	<0.001	—	—
Histidine/protein ratio (mg/g)	32.6±3.2	0.12	<0.001	—	—
Percentage of subjects (%)					
Physical activity level					
Sedentary	88	—	—	−3.74	<0.001
Physically active[d]	12				
Rate of eating				6.65[f]	<0.001
Very slow	5				
Relatively slow	23				
Medium	36				
Relatively fast	32	—	—		
Very fast	4				
Experience of dieting[g]				−0.85	0.40
No	40				
Yes	60	—	—		
Smoking habits				2.75[f]	0.06
Current	3				
Past	3	—	—		
Never	94				
Alcohol intake[h]				0.60	0.55
Non-drinker	81				
Drinker	19	—	—		

[a] Unless otherwise specified, values are expressed as mean±SD.
[b] Pearson's correlation coefficient for numerical variable.
[c] Spearman's correlation coefficient for numerical variable because of the very skewed distribution.
[d] The subjects who took part in sports club activity at least once per week were defined as physically active.
[e] t-value for difference in energy intake between categories (t-test).
[f] F-value for difference in energy intake between categories (ANOVA).
[g] Dieting by intentional reduction of body weight within 1 mo by more than 2 kg.
[h] The subjects who did not drink alcohol during the previous 1 mo were defineds as non-drinkers and the others as drinkers.

−0.0011 in Model 3). The results were similar for histidine/protein (β=−0.079 in Model 3).

DISCUSSION

In this cross-sectional study of young Japanese women aged 18 y, both crude histidine intake and the ratio of histidine to protein (histidine/protein) negatively and significantly correlated with energy intake, independent of the other dietary factors and the currently known covariates (Pearson's correlation coefficient, r=−0.22, p<0.001 for histidine crude value; r=−0.23, p<0.001 for histidine/protein). One small-scale cross-sectional study with 26 male and 38 female students has also found a negative association between histidine/protein and energy intake, but it was statistically significant only in women (r=−0.18 in men and r=−0.34, p<0.05 in women) (*14*). Therefore, our findings on the basis of data from a large and homogenous sample suggested that dietary histidine might have a suppressive effect on energy intake in human.

Among previous animal studies, a number of approaches have been tried to clarify the roles of the histamine signaling pathway in the regulation of food intake (*5, 6, 26–28*). However, the routes of histidine

Table 2. Multiple regression analysis on association between dietary histidine intake, histidine/protein and energy intake (MJ/d).[a]

	Partial regression coefficient	R^2	p-value	Pearson's partial correlation coefficient
Histidine intake (mg/d)				
Model 1[b]	0.0020	0.62	<0.001	0.79
Model 2[c]	0.0020	0.63	<0.001	0.62
Model 3[d]	−0.0011	0.75	<0.001	−0.22
Histidine/protein (mg/g)				
Model 1[b]	0.076	0.01	<0.001	0.12
Model 2[c]	0.072	0.05	<0.001	0.12
Model 3[d]	−0.079	0.75	<0.001	−0.23

[a] Partial regression coefficient, adjusted R^2, and p values are for independent variables in multiple regression.
[b] Model 1: simple regression and correlation analyses.
[c] Model 2: adjusted for body height, body weight, sports club activity level (two categories), and rate of eating.
[d] Model 3: additionally adjusted for total dietary fiber and protein excluding histidine for histidine intake. When histidine/protein ratio was used as an independent variable, total dietary fiber and protein intake were included as a covariate.

administration were almost all intracerebroventricular infusion or intraperitoneal (IP) injection (*6–9, 28*). On the other hand, the intragastric route had been examined in rats by Vaziri et al. (*8*). Although the sensitivity to the suppression of food intake was low compared to that for IP, the results suggested that dietary histidine might play a role in regulating food and water intake. The suppressive effect of dietary histidine on energy intake observed in our human study was in agreement with the result reported by Vaziri et al.

To our knowledge, studies of the effects of histidine on feeding regulation in human were conducted mostly in the 1970s (*10–12*), except for one study (*14*). Most studies suggested that feeding suppression seemed to be caused by alteration of zinc metabolism rather than the direct effects of histidine. But a large dose of histidine such as more than 4 g/d was reported to produce anorexia even without alteration of the zinc metabolism (*11, 12*). Considering the above-mentioned reports, the possibility that histidine-induced zinc deficiency affects energy intake seemed to be quite low in our study because the mean intake of histidine was about 2.1 g/d (Table 1).

Several dietary and non-dietary variables have been reported to show an association with energy intake (*23–25*). However, the previous epidemiologic studies have not taken into consideration the confounding factors that are unavoidable in epidemiologic studies. Therefore, it was nearly impossible to accept the observed negative correlation between histidine and energy intake. On the other hand, we considered the confounding factors in this study (Models 2 and 3 in Table 2). After adjustment for non-dietary factors, both histidine and histidine/protein ratio positively correlated with energy intake (r=0.62 and 0.12, respectively, p<0.001). Since physical activity is known to be associated with energy intake, we also conducted the same analyses dividing the subjects into two groups by physical activity level, i.e., sedentary or physically active. However, the results did not materially change (data not shown). As for dietary factors, because both histidine and protein highly correlated with energy intake (r=0.79 and 0.86, respectively), we entered protein intake as a covariate into the multiple regression analyses in order to avoid multicolinearity as much as possible. Moreover, we adjusted for protein excluding dietary histidine in order to minimize a possible effect of other amino acids. Dietary histidine negatively correlated with energy intake after adjustment for dietary and non-dietary confounding factors in our study. These findings provide a new insight into a role of dietary histidine in energy intake in human, although it is not enough. However, we do not know whether this model was fully appropriate for examining the association between dietary histidine and energy intake.

It is most important to understand that self-reported dietary intakes are not entirely free from reporting errors such as underreporting of energy and food intakes (*29, 30*). In this population, when we examined the validity of energy intake to basal metabolic rate (EI/BMR) (*31, 32*), 37% of subjects tended to underreport energy intake because their EI/BMR level was below the minimum survival value of 1.27 (*33*). Few studies have examined the bias in reporting nutrients and types of foods consumed (*34, 35*). Inconsistent with our results (data not shown), Livingstone and Black revealed that energy from protein tended to be significantly higher in low energy reporters (*29*). Moreover, the low energy reporters tended to report a higher consumption of "socially desirable" foods such as meat, fish, and vegetables (*29*). Therefore, the results should be cautiously interpreted in respect to underreporting of energy intake.

Our data are limited by the possibility of error with respect to the measurement of diet and the calculation of dietary histidine intake because of the lack of a comprehensive food composition table of amino acids (*19*). Therefore, when histidine content of a particular food was unavailable, we used the reported value for a similar food, as proposed by Todoriki et al. (*20*). This procedure was used for the development of the food composition table of fatty acids, and the validity was examined (*36*). However, this procedure was far below the quality required for the study. Moreover, the validity of this procedure used for amino acids has not been reported. In addition, the food composition table of amino acid substitution used in this procedure is not available to the public. Nonetheless, we considered this method as the best available at the present time in Japan. The results should be interpreted very cautiously.

Some limitations of our study should be considered in interpreting the results. First, the subjects were not a

randomly sampled general Japanese population but selected female dietetic students aged 18–20 y. Because they were freshmen who entered the dietetic course, the participants in this study might be highly health-conscious. In order to minimize the influence of nutritional education, we finished the survey within almost 1 mo after entrance into the course. Secondly, our findings came from a cross-sectional study. Therefore, it was impossible to evaluate causal association between histidine and energy intake. Moreover, epidemiologic studies can not clarify the mechanism of the effect of histidine intake on energy intake. Thirdly, the lists of food items in the DHQ, especially those of fishes, were made based on the conventional nutrients such as fats rather than histidine. The histidine intakes obtained by the DHQ in this study might have been less accurate than a direct observation by dietary record. Fourthly, the effective time, duration, and quantity of dietary histidine for regulating energy intake were not strictly clear in this study. In the case of animal studies, histidine was shown to be a regulator of short-term food intake, and the time interval for observation was designed within 24 h (*6*, *8*). We might have misunderstood the relationship between histidine and energy intake observed in this study because habitual histidine intake for the previous 1 mo was assessed in our study. Fifthly, although we adjusted for possible confounding variables, unmeasured or unknown confounding dietary factors cannot be excluded.

In conclusion, we found an inverse association between histidine/protein ratio and energy intake among young female Japanese students. Although the central roles of mechanisms for regulation of energy intake have already been established in animal and in vitro studies, the contribution of daily histidine intake is not yet fully understood in humans. Future epidemiologic studies with better study designs are warranted to examine the role of dietary histidine in energy intake in human.

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Report

Effect of Dietary Factors on Incidence of Type 2 Diabetes: A Systematic Review of Cohort Studies

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Summary We systematically reviewed cohort studies on the effect of nutrient and food intake (except for alcohol) on the incidence of type 2 diabetes, which had been published in English as of May 2004. Using the MEDLINE (PubMed) database as well as reference lists of searched papers, 15 individual cohort studies (a total of 31 papers) were identified. The number of subjects (n=895–85,060), follow-up length (5.9–23 y), the number of diabetes cases (n=74–4,085), dietary assessment method used (simple food questionnaire, food frequency questionnaire, food frequency interview, diet history interview, and 24-h recall), and method of case ascertainment (questionnaire, oral glucose tolerance test, fasting glucose level, death certificate, and nationwide registry) varied among studies. For nutrients, intakes of vegetable fat, polyunsaturated fatty acid, dietary fiber (particularly cereal fiber), magnesium, and caffeine were significantly inversely correlated and intakes of trans fatty acid and heme-iron, glycemic index, and glycemic load were significantly positively correlated with the incidence of type 2 diabetes in several papers. For foods and food groups, several papers showed significantly decreased risk for type 2 diabetes with the higher consumption of grain (particularly whole grain) and coffee, and significantly increased risk with processed meat consumption. Because all the studies were carried out in Western countries, however, research in non-Western countries including Japan is needed.

Key Words nutrient, food, type 2 diabetes, cohort study, systematic review

It is estimated that in 2000 there were about 150 million people with type 2 diabetes all over the world and that this figure will double by 2025 (*1*). While type 2 diabetes and its complications such as cardiovascular disease, amputation, blindness, and renal failure adversely affect the quality of life, there is no currently available cure for diabetes. Thus, primary prevention of the disease is of paramount importance to public health. Although many lifestyle factors are associated with the development of type 2 diabetes (*2*, *3*), food and nutrition may also play an important role in its cause (*4*). In Japan, a cohort study suggests decreased ratio of polyunsaturated to saturated fatty acids as a risk factor for glucose intolerance (*5*), although there is no cohort study where the endpoint is the incidence of diabetes.

In prevention and clinical settings, the findings in human studies are much more important than extrapolation of the results from animal studies. However, a report which systematically reviews human studies on the association between dietary factors and type 2 diabetes is not currently available. A systematic collection of previous publications (scientific papers) and its efficient application are essential for the evidence-based primary care and treatment of type 2 diabetes. We, therefore, systematically reviewed published cohort studies examining the effects of dietary factors on the incidence of type 2 diabetes. Alcohol was excluded in the present paper not only because assessment methods were quite different between alcohol and other dietary factors such as nutrient and food intake, but also because a systematic review of the relation between alcohol consumption and the risk of type 2 diabetes has been published very recently (*6*).

Materials and Methods

We searched the MEDLINE (PubMed) database for cohort studies on the relations of dietary variables including energy and nutrient intake, food consumption, and dietary score with the risk of developing type 2 diabetes using the following search strategy: ("diet" OR "dietary" OR "nutrient" OR "consumption" OR "intake") AND ("diabetes" OR "diabetic") AND ("prospective" OR "cohort" OR "follow-up"). The search was limited to English-language reports of apparently healthy persons 15 y of age or older, which were published by the end of May, 2004. We then identified papers (including review papers) on cohort studies assessing the effects of dietary factors on the incidence of type 2 diabetes by reading the abstract of each retrieved article. Of these articles and their reference lists, only articles that met all the following criteria

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were identified: 1) the endpoint was the incidence of diabetes; 2) follow-up procedure and length and the definition of the incidence of diabetes were clearly documented; 3) quantitative (including consumption frequency) assessment of food and/or nutrient was conducted; 4) results were shown using the relative risk (RR) (and 95% confidence interval (CI)); and 5) factors used when calculating multivariate RR were clearly indicated. As a result, 15 individual cohort studies (31 articles) of dietary factors and the risk of type 2 diabetes were examined in the present paper.

We retrieved from the 31 articles 1) the number of subjects, their sex, and age; 2) follow-up length; 3) procedure for ascertainment of the incidence of diabetes and the number of diabetes cases; 4) dietary assessment instrument used; 5) dietary factors examined; 6) variables used for adjustment; and 7) multivariate RR (and 95% CI) and p for trend. For dietary factors examined using more than one statistical analysis, the results of the analysis which included the largest number of factors for adjustment were retrieved. Although several articles performed stratified analyses according to several risk factors for diabetes, the analysis of all participants was retrieved whenever possible. When men and women or white and African-American were analyzed separately, we retrieved these separate analyses. The results were considered statistically significant when either of the following conditions was met: 1) the risk in the highest category was statistically significant ($p<0.05$) compared with that of the lowest category, or 2) p for trend between dietary factors and the risk of diabetes was statistically significant (<0.05).

Results

Table 1 shows all the results of the 15 cohort studies (31 articles) investigating the effect of dietary factors on the incidence of type 2 diabetes. All 15 studies were carried out in Western countries: 10 studies in the USA (studies 1–7, 9, 12, and 13 (*7–27, 29, 30, 34, 35*)); 3 in Finland (studies 10, 11, and 15 (*31–33, 37*)); 1 in the Netherlands (study 8 (*28*)); and 1 in Sweden (study 14 (*36*)). One study (study 3) investigated only male subjects, while five studies (studies 2, 5, 9, 13, and 14) examined only female subjects. Both sexes were investigated in the other nine studies; men and women were analyzed separately in three studies (studies 1, 6, and 15) while the remaining six studies (studies 4, 7, 8, 10, 11, and 12) analyzed the data of men and women combined. The age of subjects ranged from 15 to 98 y. The number of subjects examined (n=895–85,060), follow-up length (5.9–23 y), and number of cases (n=74–4,085) also varied considerably among articles.

Various methods for ascertainment of the development of diabetes were used (see footnotes to Table 1): death certificate or nationwide registry (studies 1, 10, 11, 14, and 15); questionnaire to confirm whether the definitions of diabetes were met (studies 2, 3, 9, and 13); 2-h 75 g oral glucose tolerance testing (studies 7 and 12); self-report by subjects (studies 5 and 8); blood glucose level and self-report (study 4); and documents such as hospital record and death certificate and self-report (study 6). The criteria for diabetes were also slightly different among studies: the National Diabetes Data Group (NDDG) (*38*) and the World Health Organization (WHO) (*39*) in studies 2, 3, 7, 12, and 13 except for the article by Lopez-Ridaura et al. (*14*) and the American Diabetes Association (ADA) (*40*) in studies 4 and 9 and the article by Lopez-Ridaura et al. (*14*).

Different dietary assessment methods were also applied: non-validated questionnaire (studies 1, 11, 12, 14, and 15); validated questionnaire (study 8); validated food frequency questionnaire (studies 2, 3, 5, 7, 9, and 13); validated food frequency interview (study 4); diet history interview (study 10); and a single 24-h dietary recall (study 6). Repeated dietary assessments were made in 11 articles (study 13 and most of studies 2 and 3 (*10–15, 17–20, 35*)).

A total of 99 dietary factors were examined in the 31 articles. Different factors were used for adjustment in each article, although well-known factors associated with the development of type 2 diabetes such as age, body mass index (BMI: weight (kg)/height (m)^2), smoking, alcohol consumption, physical activity, family history of diabetes, and energy intake were used in many analyses.

A summary of the results of the association of energy and nutrient intake with the risk of type 2 diabetes is shown in Table 2. Although several studies investigated the relationship of energy and macronutrients (protein, fat, and carbohydrate) to the development of type 2 diabetes, no study has shown a significant relation to date. However, several studies indicated that several types of fat and sugar appeared to be more important. Vegetable fat and polyunsaturated fatty acid were inversely associated with the incidence of type 2 diabetes in several studies, while a positive association between trans fatty acid and the risk of type 2 diabetes was observed in several studies. One study showed an inverse association between the ratio of polyunsaturated to saturated fatty acid and the incidence of type 2 diabetes. For sugars, on the other hand, a beneficial effect of sucrose and adverse effects of glucose and fructose were observed in one study. In addition, positive relations of glycemic index (a qualitative indicator of carbohydrate's ability to raise blood glucose levels) and glycemic load (an indicator of a glucose response or insulin demand induced by the total carbohydrate intake) to the risk of type 2 diabetes were found in several studies.

Several studies indicated an inverse association between dietary fiber and the incidence of type 2 diabetes. Among various types of fiber, beneficial effects of cereal fiber (in several studies), soluble fiber (in one study), and insoluble noncellulose polysaccharides (in one study) were observed. One study showed a positive relationship between cholesterol and the risk of type 2 diabetes. For minerals, several studies indicated a beneficial effect of magnesium (both diet only and diet and supplement combined) and an adverse effect of heme iron. A positive relation between heme iron from red meat and the risk of type 2 diabetes was observed in one