

Table 1 Baseline characteristics of study subjects ($n = 17,590$)

	Total subjects	HCV-antibody and HBsAg negative subjects	HCV-antibody positive and HBsAg negative subjects	HCV-antibody negative and HBsAg positive subjects	HCV-antibody and HBsAg positive subjects
Number of subjects	17,590	16,213	939	419	19
Total person-years	222,800.6	206,239.1	11,032.9	5,306.3	222.3
Age (mean)	57.0	56.9	59.4	55.6	56.6
Men (%)	34.6	34.0	42.3	42.0	31.6
Smoking status (%)					
Never	71.4	72.2	58.4	69.5	68.4
Past	11.5	11.3	15.1	11.7	5.3
Current	17.1	16.5	26.5	18.9	26.3
Weekly ethanol intake (%)					
Past	2.0	1.8	6.0	1.7	63.2
Never	61.6	62.0	55.4	59.0	5.3
<weekly	6.3	6.3	6.2	6.9	10.5
<150 g per week	15.1	14.9	17.9	14.8	10.5
150 to <300 g per week	8.1	8.1	8.9	7.6	10.5
≥ 300 g per week	6.9	6.9	5.6	10.0	0.0
Coffee intake (%)					
Almost never	33.2	33.1	35.7	31.0	31.6
1–2 days per week	19.8	19.7	21.1	18.8	10.5
3–4 days per week	10.7	10.6	10.9	14.1	5.3
1–2 cups per day	27.5	27.7	24.6	24.6	42.1
3–4 cups per day	7.1	7.1	6.2	9.1	10.5
≥ 5 cups per day	1.8	1.8	1.6	2.4	0.0
Serum total cholesterol (mg/dl) (mean)	203.4	204.5	190.0	191.1	193.2
Metabolic factors in the aggregate (%)					
≥ 3 factors	22.2	22.3	21.5	18.1	15.8
≥ 2 factors in addition to being overweight	16.1	16.3	13.7	13.1	15.8
Component of metabolic factors (%)					
High blood pressure	59.3	59.0	58.9	61.8	57.9
High glucose	20.7	20.5	23.9	21.0	21.1
Low HDL-cholesterol	23.3	23.2	26.6	19.6	15.8
High triglycerides	23.6	24.1	18.6	15.0	21.1
Overweight	30.8	31.0	25.8	32.9	52.6

attenuated and the risk of overweight was more clearly observed. Likewise, those who were negative for both HCV- and HBV infection revealed a similar tendency to those who were infection-positive, albeit without statistical significance.

Additional analysis was conducted to determine the presence of the effect of BMI and effect modification between overweight and high glucose (Table 4). Increased BMI was associated with HCC in both genders of all subjects and those with HCV infection. The association was more clearly observed in men than in women. The presence of both high glucose and overweight significantly

increased the risk of HCC, although no significant effect due to modification between overweight and high glucose level was observed.

Discussion

In this prospective cohort study among a large Japanese population, we found that the presence of metabolic factors in the aggregate predicted the subsequent risk of HCC in men, including those with HCV infection. Our results also confirmed that the main contributors to the effect of

Table 2 Hazard ratios (HRs) and 95% CIs of hepatocellular carcinoma according to the metabolic factors^a

	Number of subjects	Number of cases	Person-years	HR	(CI)
<i>Components of metabolic factors</i>					
High blood pressure					
Absent	7,156	35	90,694	1.00	
Present	10,434	67	132,107	0.97	(0.62–1.53)
High glucose					
Absent	13,950	65	177,493	1.00	
Present	3,640	37	45,307	1.75	(1.11–2.74)
Low HDL-cholesterol					
Absent	13,487	70	170,673	1.00	
Present	4,103	32	52,128	1.17	(0.72–1.92)
High triglycerides					
Absent	13,442	87	170,277	1.00	
Present	4,148	15	52,523	0.75	(0.40–1.39)
Overweight					
Absent	12,180	64	153,362	1.00	
Present	5,410	38	69,438	2.22	(1.42–3.48)
<i>Metabolic factors in the aggregate</i>					
≥3 factors					
Absent	13,692	73	173,316	1.00	
Present	3,898	29	49,485	1.68	(1.06–2.66)
≥2 factors in addition to being overweight					
Absent	14,756	81	186,608	1.00	
Present	2,834	21	36,192	2.14	(1.27–3.61)

^a Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HbsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

metabolic factors on HCC were overweight and a high glucose state.

Previous epidemiological observations on the effect of metabolic factors in the aggregate on the risk of HCC are scarce [9, 10]. Results have generally shown positive association with metabolic factors in the aggregate, although one [9] did not account for hepatitis virus infection status, and another [10] lacked information on some of the components of metabolic factors and provided results only for subjects without infection. Meanwhile, a number of epidemiological studies have implicated diabetes as a risk factor for HCC [4, 10–20]. Obesity is the most important risk factor for diabetes, and diabetes and obesity are highly related events [37]. A number of epidemiological studies have reported an association between obesity and HCC [10, 21–26], most of which found a significant positive association in men but a weaker positive association in women. The only two studies accounting for hepatitis virus infection status found a significant positive association among those with HCV infection [10, 21], albeit that results for men and women were combined.

The biological mechanism by which metabolic factors leads to HCC has not been fully clarified. One suggested candidate is that obesity leads to insulin resistance and steatosis, which are associated with the release of inflammatory mediators such as tumor necrosis factor (TNF)- α in the liver. This would in turn enhance the production of cytokines, including interleukin (IL)-6 and IL-8, leading to steatohepatitis or NASH [15]. On this basis, obesity and diabetes cause hepatic inflammation, leading to oxidative stress and lipid peroxidation, subsequently resulting in hepatic injury, fibrosis, and eventual cirrhosis and HCC [37]. Several studies have also suggested a synergistic effect of diabetes with viral hepatitis [20] and alcohol intake [15, 16, 20].

It is also known that the liver plays a key role in serum lipoprotein synthesis and metabolism, and impaired lipid metabolism is often found in patients with chronic liver diseases [38]. This finding is supported by several cross-sectional studies among HCV-positive subjects [39, 40]. With metabolic syndrome, free fatty acids (FFAs) are released in abundance from an expanded adipose tissue

Table 3 Hazard ratios and 95% CIs of hepatocellular carcinoma according to metabolic factors by hepatitis viral infection status^a

	HCV-antibody positive subjects				HCV-antibody and HBsAg negative subjects			
	Number of subjects	Number of cases	Person-years	HR (CI)	Number of subjects	Number of cases	Person-years	HR (CI)
<i>Components of metabolic factors</i>								
High blood pressure								
Absent	346	26	4,113.2	1.00	6,650	7	84,548.0	1.00
Present	612	47	7,142.0	0.98 (0.56–1.72)	9,563	11	121,691.1	0.60 (0.21–1.70)
High glucose								
Absent	730	48	8,678.0	1.00	12,889	10	164,622.3	1.00
Present	228	25	2,577.2	1.49 (0.85–2.61)	3,324	8	41,616.8	2.48 (0.93–6.60)
Low HDL-cholesterol								
Absent	705	48	8,346.6	1.00	12,445	14	158,055.8	1.00
Present	253	25	2,908.6	1.18 (0.65–2.16)	3,768	4	48,183.3	0.63 (0.18–2.17)
High triglycerides								
Absent	779	63	9,117.6	1.00	12,307	13	156,661.8	1.00
Present	179	10	2,137.6	0.64 (0.30–1.39)	3,906	5	49,577.3	2.14 (0.64–7.18)
Overweight								
Absent	706	44	8,335.5	1.00	141,479	11	11,883.0	1.00
Present	252	29	2,919.7	2.66 (1.54–4.62)	64,760	7	4,678.5	1.81 (0.64–5.07)
<i>Metabolic factors in the aggregate</i>								
≥3 factors								
Absent	753	51	8,850.8	1.00	12,596	12	160,133.1	1.00
Present	205	22	2,404.4	1.83 (1.05–3.18)	3,617	6	46,106.0	1.80 (0.65–4.98)
≥2 factors in addition to being overweight								
Absent	826	57	9,710.2	1.00	13,556	14	172,296.2	1.00
Present	132	16	1,545.0	2.57 (1.37–4.80)	2,647	4	33,942.9	1.79 (0.57–5.63)

^a Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150–<300 g per week, ≥300 g per week), coffee intake (never, 1–2 cups/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HBsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

Table 4 Hazard ratios and 95% CIs of hepatocellular carcinoma according to body mass index and glucose level status^a

	Total subjects				HCV-antibody positive subjects				HCV-antibody and HBsAg negative subjects			
	Number of subjects	Number of cases	Person-years	HR (CI)	Number of subjects	Number of cases	Person-years	HR ^a (CI)	Number of subjects	Number of cases	Person-years	HR (CI)
<i>Body mass index</i>												
<25	12,180	64	153,362.4	1.00	704	44	8,335.5	1.00	11,193	11	141,479.4	1.00
25 to <27	2,903	21	37,183.2	2.07 (1.22–3.52)	150	16	1,690.6	2.55 (1.34–4.85)	2,684	4	34,619.2	1.91 (0.59–6.14)
≥27	2,507	17	32,255.0	2.72 (1.51–4.89)	102	13	1,229.1	3.08 (1.51–6.30)	2,336	3	30,140.5	1.84 (0.48–7.04)
<i>p for trend</i>				0.019				0.017				0.414
<i>Overweight</i>												
Absent	9,874	43	124,802.5	1.00	550	29	6,549.6	1.00	9,101	8	115,441.0	1.00
Present	2,306	21	52,690.9	1.57 (0.88–2.79)	156	15	1,785.9	1.75 (0.86–3.58)	2,092	3	26,038.4	1.14 (0.28–4.62)
Absent	4,076	22	28,559.9	2.01 (1.16–3.49)	180	19	2,128.4	3.06 (1.59–5.88)	3,788	2	49,181.3	0.77 (0.16–3.69)
Present	1,334	16	16,747.3	4.10 (2.19–7.69)	72	10	791.3	3.36 (1.47–7.68)	1,232	5	15,578.4	5.14 (1.60–16.55)
<i>p for interaction between high glucose and overweight</i>				0.620				0.369				0.121

^a Adjusted for age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 cups/week, 3–4 cups/week, every day (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous), and HCV infection status (anti-HCV antibody-negative, -positive) and HBV infection status (HBsAg-negative, -positive)

mass. In the liver, FFAs produce an increased production of glucose, triglycerides, and secretion of very low density lipoproteins (VLDL), with lipid/lipoprotein abnormalities such as reductions in HDL-cholesterol and an increased density of low density lipoprotein (LDL) [8]. This VLDL secretion and fatty acid β -oxidation, may in turn, result in increased triglyceride synthesis in the liver [41, 42]. A similar mechanism may also be involved in the association between metabolic factors and HCC. In this study, however, the positive association between low HDL-cholesterol and risk of HCC was not significant.

Based on this study, we speculate that metabolic factors may affect the risk of HCC not only in those with hepatitis virus infection but also without hepatitis virus infection, via a common or different pathway. More specifically, metabolic factors may play a role in those without hepatitis virus infection through NASH/NAFLD and related conditions, and in promoting carcinogenesis after infection. Nevertheless, our analyses among both HCV- and HBV infection-negative subjects were based on a small number of cases, meaning no definite conclusions can be drawn, and any interpretation requires caution. In addition, clinical investigations have shown that most HCC in this population originates from HCV- or HBV infection [7], and that the proportion of non-B/non-C HCC in all HCC has been reported to be around 10–12% since 1999 [43]. In addition, a small proportion of NAFLD/NASH patients develop HCC [44]. Together, these findings imply that the contribution of factors other than hepatitis virus infection such as NASH/NAFLD in this population may not be large, at the present time at least. However, given the increasing trend in the incidence of HCC unrelated to hepatitis virus infection, the contribution of metabolic factors among the overall etiology, if any, will soon likely increase. The small number of cases prevented us from restricting analysis to HBV-positive subjects, and is a limitation of this study. Whether the effect of metabolic factors on HCC differs between those positive and negative for hepatitis virus infection, and between those positive for HCV and for HBV, is not conclusive for lack of consistency between studies.

The major strength of this study is its prospective design, in which information was collected before the subsequent diagnosis of HCC, thereby avoiding the exposure recall bias inherent with case-control studies. Other strengths include: study subjects were selected from the general population; the proportion of loss to follow-up (0.3%) was negligible; the quality of our cancer registry system was satisfactory over the study period; and potential confounding factors could be adjusted to minimize their influence on risk values, in spite of the possible influence of residual confounding.

Against this, several obvious limitations can be identified. First, waist circumference was not available to assess

exposure. However, given previous studies that a BMI of 25.0 kg/m² was equal to 100 cm² of visceral fat area as central obesity [32], misclassification by the use of BMI instead of waist circumference, if any, might be small. Likewise, we used non-fasting data, in particular non-fasting triglycerides ≥ 1.69 mmol/l (150 mg/dl), as a component of the metabolic factors, although justification for the use of the same cut-off point as for fasting status is presently under debate. In this study, nevertheless, analyses limited to fasting subjects yielded closely similar results.

Second, evaluation by single measurement of components of metabolic factors at baseline might have produced misclassification, even though this would likely have been non-differential and might lead to an underestimation of results. Further, the subjects of this study were restricted to 26% of the total study subjects with complete questionnaire responses and health checkup data. More women than men tend to participate in health checkup surveys provided by local governments. Further, participants often differ from nonparticipants in socioeconomic status and have a more favorable lifestyle profile, such as lower smoking rates, greater participation in physical exercise, and higher intake of green vegetables and fruits, particularly women [45, 46]. Differences in these factors may have influenced the association between metabolic factors and HCC. In addition, the incidence of HCC in this study population during the follow-up period was 45.7 per 100,000 person-years versus 67.5 in the whole JPHC Study, suggesting that subjects who were already under care for hepatitis virus infection or any of the components of metabolic factors may have been less willing to attend a health checkup. Together, these considerations mandate the need for caution in interpreting or generalizing these results.

Allowing for these methodological issues, metabolic factors in the aggregate may have been associated with an increased risk of HCC in the study population. The effects of overweight and high glucose state appear to have been the main contributors to this association, even under the condition of HCV infection. Our results imply the need to include obesity and diabetes as a crucial target in preventing progression to HCC, even among those already infected with HCV.

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Appendix

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S.

Tsugane) Group are: S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, A. Okayama, and Y. Kokubo, National Cardiovascular Center, Osaka; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Iwate; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, and N. Nagai, Akita Prefectural Yokote Public Health Center, Akita; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, and Y. Kobayashi, Nagano Prefectural Saku Public Health Center, Nagano; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irci, and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji, and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Ibaraki; K. Matsui, T. Abe, M. Katagiri, M. Suzuki, and K. Matsui, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata; M. Doi, A. Terao, Y. Ishikawa, and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi; H. Sueta, H. Doi, M. Urata, N. Okamoto, and F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki; H. Sakiyama, N. Onga, H. Takaesu, and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano, Osaka Prefectural Suita Public Health Center, Osaka; Y. Tsubono, Tohoku University, Miyagi; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Honda, K. Yamagishi, and S. Sakurai, Tsukuba University, Ibaraki; M. Kabuto, National Institute for Environmental Studies, Ibaraki; M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; M. Akabane, Tokyo University of Agriculture, Tokyo; T. Kadowaki, Tokyo University, Tokyo; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; Y. Takashima, Kyorin University, Tokyo; K. Nakamura, Niigata University, Niigata; S. Matsushima and S. Natsukawa, Saku General Hospital, Nagano; H. Shimizu, Sakihae Institute, Gifu; H. Sugimura, Hamamatsu University, Shizuoka; S. Tominaga, Aichi Cancer Center Research Institute, Aichi; H. Iso, Osaka University, Osaka; M. Iida, W. Ajiki, and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; E. Maruyama, Kobe University, Hyogo; M. Konishi, K. Okada, and I. Saito, Ehime University, Ehime; N. Yasuda, Kochi University, Kochi; S. Kono, Kyushu University, Fukuoka.

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Psychological Factors, Coffee and Risk of Diabetes Mellitus among Middle-Aged Japanese: a Population-Based Prospective Study in the JPHC Study Cohort

MASAYUKI KATO*, MITSUHIKO NODA**, MANAMI INOUE***, TAKASHI KADOWAKI[#],
SHOICHIRO TSUGANE***; for the JPHC Study Group

* Japan Foundation for the Promotion of International Medical Research Cooperation, 1-21-13 Toyama, Shinjuku-ku, Tokyo 162-0052, Japan

** Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

*** Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

[#] Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Abstract. An association between psychological factors and diabetes has been suspected for a long time. However, epidemiological data on this association is limited. We investigated the association between psychological factors (perceived mental stress and type A behavior) and the onset of diabetes in a community-based, prospective cohort study in a large number of middle-aged Japanese adults. A total of 55,826 subjects (24,826 men and 31,000 women) aged 40-69 years were followed for 10 years. A self-administered questionnaire on medical conditions including diabetes and other lifestyle factors was performed at baseline and 5 and 10 years later. Psychological factors and diabetes were assessed based on the questionnaire results. During the 10-year follow-up period, we documented 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women. The risk of diabetes increased with an increasing stress level, especially among men. Multivariate adjusted odds ratios for high stress compared with low stress were 1.36 (1.13 to 1.63) among men and 1.22 (0.98 to 1.51) among women. The risk of diabetes increased with an increasing level of type A behavior only among women. Multivariate adjusted odds ratios for high levels of type A behavior compared with low levels of type A behavior were 1.09 (0.94 to 1.27) among men and 1.22 (1.01 to 1.47) among women. We found an association between perceived mental stress and the incidence of diabetes, especially among men. We also found an association between type A behavior and the incidence of diabetes among women. In addition, inverse association between coffee consumption and the incidence of diabetes which was consistent with other studies was observed.

Key words: diabetes mellitus, perceived mental stress, type A behavior, coffee

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THE PREVALENCE of type 2 diabetes has increased dramatically over the past few decades. Recent estimates indicate that there were 171 million people with diabetes worldwide in the year 2000 and this number

is projected to increase to 366 million by 2030 [1]. Diabetes is now one of the main threats to human health and is likely to remain a huge threat to public health in years to come [2].

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Correspondence to: Mitsuhiro NODA, Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

Abbreviations: HPA, hypothalamus-pituitary-adrenal; JPHC study, The Japan Public Health Centre-based prospective Study; IL-6, interleukin-6; OR, odds ratio; 95% CI, 95% confidence interval.

An association between psychological factors and diabetes has long been suspected [3, 4]. For example, mental stress is thought to deteriorate glucose metabolism through the activation of the hypothalamus-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system [5-8]. Type A behavior pattern is also thought to activate the HPA axis and the sympathetic nervous system. However, epidemiological data about

the association between these psychological factors and diabetes is limited [9-13], and, as far as we know, no study has shown an association between these factors and the incidence of diabetes in a general population. In this paper, we examined the effect of psychological factors (mental stress and type A behavior) on the incidence of diabetes mellitus in a community-based, prospective cohort study in a large number of middle-aged Japanese adults.

Materials and Methods

Subjects and procedures

The Japan Public Health Centre-based prospective Study (JPHC Study) is an ongoing, longitudinal cohort study investigating cancer, cardiovascular diseases and other lifestyle-related diseases. The JPHC Study was launched in 1990 for cohort I and in 1993 for cohort II. Cohort I was composed of five prefectural public health center areas; Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo). Cohort II was composed of six prefectural public health center areas; Mito (Ibaraki Prefecture), Nagaoka (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture), and Suita (Osaka Prefecture). The details of the study design have been described elsewhere [14]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, two public health center areas (Katsushika and Suita) were excluded because different definitions for the study population were applied. The study population was defined as all registered Japanese inhabitants of the nine public health center areas aged 40-59 years (Cohort I) and 40-69 years (Cohort II) at the beginning of each baseline survey. Each participant completed a self-administered questionnaire that included questions about weight, height, previously diagnosed medical conditions, family history of diabetes, use of drugs, and other lifestyle factors such as physical activity and smoking. This questionnaire also included a food frequency questionnaire that was validated using 28-day diet records [15]. The questionnaire was performed at baseline and 5 and 10 years later. Of the 95,373 individuals (45,452 men and 49,921 women) who completed

the baseline questionnaire upon enrolment, 71,713 (75%, 32,369 men and 39,344 women) responded to both of the follow-up questionnaires. We excluded individuals who had any of the following conditions at baseline; cardiovascular disease, chronic liver disease, kidney disease or any type of cancer (n=4,515). Individuals who had missing baseline data for any of the exposure parameters described below were also excluded (n=9,256). Individuals with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 14 or more than 40 were also excluded because of the possibility of unreliable data (n=741). Because the present study examined the incidence of diabetes, we also excluded any subjects with diabetes at baseline (n=3,092). After these exclusions, the remaining cohort consisted of 55,826 participants (24,826 men and 31,000 women).

Assessment of Psychological factors and diabetes

Mental stress was assessed based on three levels of response (low, medium and high) to the question, 'How much stress do you feel in your daily life?' We assessed four aspects of the type A behavioral pattern through self-reports of: competitive drive, speed and impatience, aggressiveness and irritability [16]. These items were assessed by the level (very, somewhat, or not at all) for each question: 'How hasty and impatient do you consider yourself to be?', 'How competitive and eager to excel in everything do you consider yourself to be?', 'How aggressive do you consider yourself to be?', and 'How irritable do you consider yourself to be?'. The above four items were scored from 0 ("not at all") to 2 ("very") and then combined into an overall index of type A behavior pattern. These items matched well with validated instruments such as the Framingham Type A Scale and MMPI-2 Type A Scale in domains such as aggression, irritability, competitiveness and time urgency [16].

We defined subjects with diabetes (diagnosed diabetes) as those who answered 'yes' to the question 'Has a doctor ever told you that you have diabetes?' or 'Do you take any anti-diabetic drugs?'. To document the validity of the diagnosed diabetes, we examined a series of medical records: 94% of the cases of diagnosed diabetes according to the questionnaire were confirmed by medical records [17]. We also conducted a cross-sectional survey in 1990 to examine the sensitivity of diagnosed diabetes according to the criteria

Table 1a. Baseline characteristics of the analysis group according to stress levels.

	Men (n=24,826)			Women (n=31,000)		
	Perceived Mental Stress			Perceived Mental Stress		
	Low (n=3,405)	Medium (n=15,734)	High (n=5,687)	Low (n=4,865)	Medium (n=20,416)	High (n=5,719)
Age	53.3	51.4	48.2	52.9	51.6	49.1
Body Mass Index	23.7	23.5	23.5	23.6	23.5	23.2
Current smoker	49.2	50.2	55.0	3.9	3.9	6.8
Alcohol drinkers*	66.1	67.4	70.1	10.1	9.5	14.0
Alcohol intake among drinkers (g/week)	270.9	264.9	265.9	79.6	79.0	88.4
Family history of diabetes (yes)	8.3	7.9	10.6	8.6	8.4	10.4
Physical activity (yes)	22.0	18.3	17.1	22.0	16.6	13.0
History of hypertension (yes)	17.3	17.2	16.7	16.0	16.5	14.9
Coffee (≥ 3 cups/day)	12.3	11.5	19.1	8.6	7.9	13.3
Hours of sleep	7.6	7.5	7.2	7.3	7.2	6.9
Level of Type A behavior pattern index						
1 (most Type A)	21.3	22.1	36.1	12.1	13.6	26.5
2	15.7	16.2	16.8	13.6	15.3	18.7
3	35.2	42.0	28.2	39.3	46.7	30.9
4 (most Type B)	27.8	19.7	18.9	35.0	24.5	23.9

Age, body mass index, alcohol intake and hours of sleep are represented as the mean, and the other variables are proportion (%).

*Alcohol drinkers: drinking alcohol ≥ 1 day/week

at that time for subjects (health checkup participants) whose plasma glucose data were available. Among the 6,118 subjects, 248 subjects had diagnosed diabetes. Among the 5,927 subjects who did not have diagnosed diabetes, 49 subjects (0.83%) had diabetes according to the commonly used diagnostic standards utilized in Japan in 1990 (fasting plasma glucose ≥ 7.8 mmol/L; casual plasma glucose ≥ 11 mmol/L) [18] based on a single measurement. Taking into account the above mentioned positive predictive value, the sensitivity and specificity of diagnosed diabetes were 82.9% and 99.7%, respectively.

Those who did not have diagnosed diabetes at baseline but who had it at the time of either the 5- or 10-year follow-up questionnaire were defined as incident cases of diabetes.

Statistical Analysis

All analyses were performed using the data from the 55,826 individuals (24,826 men and 31,000 women) who responded to both the 5- and 10-year questionnaires. The cumulative incidence was defined as the number of new cases of diabetes occurring during the 10-year follow up period divided by the number of subjects at risk of developing diabetes at baseline. We carried out a multivariate analysis using logistic

regression to assess the risk of diabetes as odds ratios adjusted for potential confounding factors such as age (continuous), body mass index (continuous), smoking status (never smoker, past smoker, or current smoker at < 20 or ≥ 20 cigarettes per day), alcohol intake (non- or infrequent occasional drinkers, or regular drinkers categorized according to weekly alcohol intake), family history of diabetes (at least one parent or one sibling with diabetes), physical activity (participation in sports at least once a week), history of hypertension, and coffee consumption (< 3 or ≥ 3 cups of coffee per day). Type A behavioral pattern was categorized into four groups based on the overall index of type A behavior pattern: very high (scores of 6–8), high (score of 5), medium (score of 4) or low (scores of 0–3). Hours of sleep was also included in the multivariate analysis as categorical variables (≤ 5 , 6, 7, 8, and ≥ 9 hours) because this factors may be associated with psychological factors. All analyses were performed separately for men and women.

Results

The baseline characteristics of the analyzed subjects according to stress levels and type A behavioral pattern index are shown in Table 1a and 1b, respec-

Table 1b. Baseline characteristics of the analysis group according to levels of Type A behavior pattern index.

	Men (n=24,826)				Women (n=31,000)			
	Levels of Type A behavior pattern index				Levels of Type A behavior pattern index			
	1 (most Type A) (n=6,253)	2 (n=4,043)	3 (n=9,408)	4 (n=5,122)	1 (n=4,886)	2 (n=4,847)	3 (n=13,206)	4 (n=8,061)
Age	50.4	50.8	51.5	50.8	50.5	50.9	52.0	51.1
Body Mass Index	23.6	23.5	23.5	23.5	23.3	23.3	23.4	23.7
Current smoker	53.2	51.5	51.1	48.7	7.3	4.7	3.7	3.7
Alcohol drinkers*	71.4	69.2	67.4	64.2	14.5	12.1	8.8	9.5
Alcohol intake among drinkers (g/week)	290.5	276.0	250.9	253.3	104.7	76.5	72.3	77.6
Family history of diabetes (yes)	9.0	8.8	7.8	9.2	10.1	9.1	8.2	8.8
Physical activity (yes)	19.8	20.3	18.0	16.5	16.9	18.0	16.8	15.9
History of hypertension (yes)	19.2	16.9	16.5	15.8	15.7	16.6	16.4	15.8
Coffee (≥ 3 cups/day)	15.0	13.1	12.3	13.4	11.3	10.1	8.2	8.4
Hours of sleep	7.4	7.5	7.4	7.4	7.1	7.2	7.2	7.1
Perceived Mental Stress								
Low	11.6	13.2	12.7	18.5	12.1	13.7	14.5	21.1
Medium	55.6	63.1	70.2	60.6	56.9	64.3	72.1	61.9
High	32.8	23.7	17.1	20.9	31.0	22.0	13.4	17.0

Age, body mass index, alcohol intake and hours of sleep are represented as the mean, and the other variables are proportion (%).

*Alcohol drinkers: drinking alcohol ≥ 1 day/week

tively. Compared with the subjects who reported low stress, those who reported higher stress were likely to be younger, smokers, physically inactive and coffee drinkers. Compared with the subjects with low levels of type A index, those with higher levels of type A index were likely to be smokers, alcohol drinkers and coffee drinkers.

During the 10-year follow-up period, we documented 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women. The age- and multivariate-adjusted odds ratios for the incidences of diabetes mellitus according to perceived mental stress are shown in Table 2. For men, a significant, dose-response association was observed between perceived mental stress and diabetes. This association remained almost unchanged after adjustments for known risk factors of diabetes, type A and hours of sleep. For women, the risk of diabetes also increased as the stress level increased. However, this association and dose-response relation were slightly weakened after adjustments for known risk factors of diabetes and margin-

ally disappeared after further adjustments for type A and hours of sleep.

The age- and multivariate-adjusted odds ratios for the incidences of diabetes mellitus according to type A index are shown in Table 3. For men, association between type A index and the risk of diabetes was not observed after adjustments for other risk factors of diabetes. For women, risk of diabetes was higher for those with highest level of type A behavior and this association was slightly strengthened after adjustments for known risk factors of diabetes, perceived mental stress and hours of sleep.

As for individual components of type A behavior pattern, high level of impatience, irritability and aggressiveness were associated, although not statistically significant, with the risk of diabetes (Table 4).

Recently, a number of papers have reported the protective effect of coffee against diabetes, and we included coffee consumption as a known risk factor of diabetes in the above analysis. In fact, coffee consumption (≥ 3 cups of coffee/day) reduced the risk of diabe-

Table 2. Odds ratios for the 10-year incidences of diabetes mellitus according to perceived mental stress
Men

	Perceived Mental Stress			p for trend
	Low (n=3,405)	Medium (n=15,734)	High (n=5,687)	
Cases	199	999	403	
Odds ratio (95%CI)				
Age-adjusted OR	1 (reference)	1.14 (0.97-1.33)	1.38 (1.15-1.65)	< 0.001
Multivariate OR ¹	1 (reference)	1.20 (1.02-1.41)	1.39 (1.16-1.67)	< 0.001
Multivariate OR ²	1 (reference)	1.19 (1.01-1.40)	1.36 (1.13-1.63)	0.001

Women

	Perceived Mental Stress			p for trend
	Low (n=4,865)	Medium (n=20,416)	High (n=5,719)	
Cases	163	720	210	
Odds ratio (95%CI)				
Age-adjusted OR	1 (reference)	1.11 (0.94-1.32)	1.28 (1.04-1.58)	0.020
Multivariate OR ¹	1 (reference)	1.11 (0.93-1.33)	1.25 (1.01-1.56)	0.038
Multivariate OR ²	1 (reference)	1.12 (0.94-1.34)	1.22 (0.98-1.51)	0.080

Multivariate OR¹: adjusted for age + other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption)

Multivariate OR²: adjusted for age + other known risk factors of diabetes + levels of Type A behavior and hours of sleep.

Table 3. Odds ratios for the 10-year incidences of diabetes mellitus according to levels of Type A behavior pattern index
Men

	Levels of Type A behavior pattern (4 = most Type B, 1 = most Type A)				p for trend
	4 (n=5,122)	3 (n=9,408)	2 (n=4,043)	1 (n=6,253)	
Cases	313	599	249	440	
Odds ratio (95%CI)					
Age-adjusted OR	1 (reference)	1.03 (0.90-1.19)	1.01 (0.85-1.20)	1.17 (1.01-1.36)	0.038
Multivariate OR ¹	1 (reference)	1.06 (0.92-1.23)	1.02 (0.85-1.21)	1.12 (0.96-1.31)	0.20
Multivariate OR ²	1 (reference)	1.06 (0.91-1.22)	1.00 (0.84-1.20)	1.09 (0.94-1.27)	0.381

Women

	Levels of Type A behavior pattern (4 = most Type B, 1 = most Type A)				p for trend
	4 (n=8,061)	3 (n=13,206)	2 (n=4,847)	1 (n=4,886)	
Cases	292	428	169	204	
Odds ratio (95%CI)					
Age-adjusted OR	1 (reference)	0.86 (0.74-1.00)	0.97 (0.80-1.18)	1.19 (0.99-1.43)	0.044
Multivariate OR ¹	1 (reference)	0.93 (0.80-1.09)	1.05 (0.86-1.27)	1.25 (1.03-1.50)	0.014
Multivariate OR ²	1 (reference)	0.93 (0.79-1.09)	1.03 (0.85-1.26)	1.22 (1.01-1.47)	0.031

Multivariate OR¹: adjusted for age + other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption)

Multivariate OR²: adjusted for age + other known risk factors of diabetes + perceived mental stress and hours of sleep.

Table 4. Odds ratios for the 10-year incidences of diabetes mellitus according to levels of constituent items of Type A behavior pattern index

Men		Low	Medium	High
Impatience	n	2,932	14,829	7,065
	cases	195	942	464
	Odds ratio (95%CI)	1 (reference)	1.01 (0.85-1.18)	1.02 (0.86-1.22)
Irritability	n	3,024	14,584	7,218
	cases	179	921	501
	Odds ratio (95%CI)	1 (reference)	1.08 (0.92-1.28)	1.14 (0.95-1.37)
Aggressiveness	n	2,885	17,118	4,823
	cases	167	1,079	355
	Odds ratio (95%CI)	1 (reference)	1.05 (0.89-1.25)	1.12 (0.92-1.36)
Competitiveness	n	2,405	17,388	5,033
	cases	172	1,081	348
	Odds ratio (95%CI)	1 (reference)	0.87 (0.73-1.03)	0.90 (0.74-1.09)
Women		Low	Medium	High
Impatience	n	4,391	19,491	7,118
	cases	160	665	268
	Odds ratio (95%CI)	1 (reference)	1.05 (0.88-1.26)	1.23 (1.00-1.51)
Irritability	n	2,931	22,312	5,757
	cases	107	762	224
	Odds ratio (95%CI)	1 (reference)	0.99 (0.80-1.23)	1.16 (0.91-1.48)
Aggressiveness	n	4,738	21,755	4,507
	cases	155	757	181
	Odds ratio (95%CI)	1 (reference)	0.96 (0.80-1.15)	1.08 (0.87-1.36)
Competitiveness	n	4,101	23,261	3,638
	cases	155	804	134
	Odds ratio (95%CI)	1 (reference)	0.99 (0.83-1.19)	1.01 (0.80-1.29)

adjusted for age, other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension and coffee consumption), perceived mental stress and hours of sleep

Table 5. Odds ratios for the 10-year incidences of diabetes mellitus according to coffee consumption

Men		n	cases	Odds Ratio	(95% CI)
almost never (reference)		7,378	540	1	
1-2 days per week		4,703	314	0.93	(0.80-1.08)
3-4 days per week		3,012	184	0.84	(0.71-1.01)
1-2 cups/day		6,417	374	0.84	(0.73-0.97)
3-4 cups/day		2,442	138	0.83	(0.68-1.02)
≥5 cup/day		874	51	0.82	(0.60-1.11)
p for trend				0.006	
Women		n	cases	Odds Ratio	(95% CI)
almost never (reference)		9,873	429	1	
1-2 days per week		5,975	218	0.90	(0.76-1.06)
3-4 days per week		3,515	127	0.95	(0.77-1.17)
1-2 cups/day		8,836	262	0.81	(0.69-0.96)
3-4 cups/day		2,223	48	0.62	(0.45-0.84)
≥5 cup/day		578	9	0.40	(0.20-0.78)
p for trend				<0.001	

adjusted for age, other known risk factors of diabetes (body mass index, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension), perceived mental stress, levels of Type A behavior and hours of sleep

tes in the present analysis, especially among women [odds ratio and 95% confidence interval were 0.91 (0.77-1.08) for men and 0.63 (0.47-0.83) for women] and there exists dose-response relationship (Table 5). Because coffee is also thought to have a psychological effect as described later in the Discussion section, we also conducted an analysis stratified according to coffee consumption (<3 or \geq 3 cups of coffee/day). After adjustments for all of the above-described parameters, the odds ratio (and 95% CI) for medium and high stress compared with low stress were 1.23 (1.03-1.46) and 1.42 (1.16-1.73) for subjects consuming <3 cups of coffee/day (p for trend = 0.001) and 0.93 (0.58-1.47) and 1.01 (0.61-1.67) for subjects consuming \geq 3 cups of coffee/day (p for trend = 0.836) for men. For women, these values were 1.14 (0.95-1.37) and 1.20 (0.96-1.51) for subjects consuming <3 cups of coffee/day (p for trend = 0.118) and 0.80 (0.36-1.75) and 1.24 (0.53-2.87) for subjects consuming \geq 3 cups of coffee/day (p for trend = 0.427). The association between perceived mental stress and diabetes was observed only among subjects who consumed <3 cups of coffee/day, especially among men. No such effect modification was observed for type A behavior pattern.

Discussion

We found that perceived mental stress was positively associated with the incidence of diabetes mellitus. The association between perceived mental stress and the incidence of diabetes mellitus was evident among men and it was statistically significant after adjustments for known risk factors of diabetes and also after further adjustments for type A behavior and hours of sleep. For women, the association between perceived mental stress and the incidence of diabetes mellitus was slightly weakened after adjustments for known risk factors of diabetes and it was marginally lower than the significant level after further adjustments for type A behavior and hours of sleep. We also found an association between type A behavior and the incidence of diabetes mellitus. In contrast to mental stress, this association was statistically significant only among women. The reason for this difference is unclear. However, one possible explanation is that there could be a difference between men and women in terms of the mutual modification between mental stress and the type A behavior, on the hypothetical basis that the

overall mechanisms by which mental stress and type A behavior give rise to diabetes may be overlapping, as discussed below, and may possibly be modifying each other.

An association between mental stress and diabetes has long been suspected [3, 4]. The mechanism by which mental stress causes diabetes is unclear, but the activation of two systems, the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system, are suspected to play roles [8, 19]. Activation of the HPA axis and the sympathetic nervous system increases secretion of cortisol and catecholamines, and hence, leads to the deterioration of glucose metabolism. Interleukin-6 (IL-6), which is suspected to play a pathologic role in a range of diseases including diabetes, is secreted during stress and participates in the stress response [20]. In fact, Kiecolt-Glaser reported an association, in caregivers, between chronic stress and increased plasma levels of IL-6 [21]. Other mechanisms such as stress induced activation of inflammatory response and the failed downregulation of corticosteroid production, have also been proposed [22].

Type A behavior is also thought to stimulate the HPA axis and the sympathetic nervous system [23] and an association between type A behavior and hyperglycemia was reported in a few studies [24, 25]. Therefore it is possible that type A behavior is associated with the risk of diabetes; however, there are no papers that report this association as far as we know.

We found an inverse association between coffee consumption and the incidence of diabetes which was consistent with other studies. Similar inverse association between green tea consumption and the incidence of diabetes was also reported [26]. We also analyzed the effect of other beverages such as green tea, black tea or oolong tea; however, we found no clear association between the risk of diabetes and consumption of these beverages. These differences may come from the fact that these beverages contain less functional ingredients than coffee.

We also found a possible effect modification of perceived mental stress by coffee consumption, especially among men. Coffee consumption may have modified the effect of mental stress on diabetes. One possible explanation for the interaction between stress and coffee consumption is that coffee blocks cortisol formation by inhibiting 11 β -hydroxysteroid dehydrogenase type 1 activity [27]. In addition, an effect modification between mental stress and coffee was reported in

the case of blood pressure, that is, coffee blunts stress-induced blood pressure increase in habitual coffee drinkers [28]. However, further research on the mechanism of this effect modification, including whether it actually exists, is needed.

The strengths of our study were that (a) it was population-based; (b) it had a relatively large cohort size; (c) it had an adequate follow-up period; and (d) the study measured and included possible confounding factors. Nevertheless, our study also had several limitations. First, the assessment of diabetes mellitus was based on the results of a self-reported questionnaire. As mentioned in the methods section, however, 94% of the diagnosed diabetes identified by this questionnaire were confirmed by medical records, and the sensitivity and specificity of the diagnosed diabetes were 82.6% and 99.7%, respectively. Therefore we think that this assessment procedure was well validated. In previous studies [17, 29] we provided different numbers for these percentages based on the current (since 1999 in Japan) diagnostic criteria [30] to evaluate the usefulness of the self-reported method for detecting real diabetic conditions using the current diagnostic criteria. In this paper, diabetes was diagnosed according to the criteria at that time (year 1990) [18] and this method is appropriate for assessing the reporting validity of diabetes diagnosed in 1990.

Second, perceived mental stress was assessed based on a single simple question, 'How much stress do you feel in your daily life?' The same question was used to investigate the association between mental stress and mortality from cardiovascular disease [31] and colorectal cancer [32]. Similar self-reported stress has been used to examine the association between stress and diseases such as breast cancer [33], stroke [34] and suicide [35]. However, more extensive stress evaluation may reveal the association between mental stress and the incidence of diabetes more precisely, which necessitates future studies.

Several sources of potential bias exist in our study. The follow-up bias does not seem to be important because the follow up percentage (75%) was relatively high and no large differences in the major risk factors for diabetes were observed between the follow-up subjects and the lost-to-follow-up subjects at baseline (for stress, 16% and 64% of the follow-up subjects and 17% and 63% of the lost-to-follow-up subjects reported low and medium stress, respectively). Misclassification with regard to diabetes and exposure

might also have caused biases. However, this type of bias in a cohort study generally distorts the results toward null.

Despite these limitations, as far as we know, our study is the first to demonstrate an association between psychological factors and the onset of diabetes in a large-scale cohort study.

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The sponsor of this study had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Approval

This study was approved by the institutional review board of the National Cancer Centre of Japan.

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ORIGINAL ARTICLE

Taste preferences and body weight change in Japanese adults: the JPHC Study

Y Matsushita¹, T Mizoue¹, Y Takahashi², A Isogawa³, M Kato⁴, M Inoue⁵, M Noda² and S Tsugane⁵ for the JPHC Study Group⁶

¹Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Shinjuku-ku, Tokyo, Japan; ²Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, Shinjuku-ku, Tokyo, Japan; ³Diabetes Care Division, Department of Internal Medicine, Mitsui Memorial Hospital, Chiyoda-ku, Tokyo, Japan; ⁴Japan Foundation for the Promotion of International Medical Research Cooperation, Shinjuku-ku, Tokyo, Japan and ⁵Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Chuo-ku, Tokyo, Japan

Objective: Limited data are available with regard to longitudinal changes in body weight by food taste preference. Here, we examined the associations between taste preferences and weight change in adults for a large-scale cohort study in Japan.

Design: Longitudinal analysis of data from a population-based cohort study, the Japan Public Health Center-based Prospective Study (JPHC Study).

Subjects: A total of 29 103 middle-aged men and women, who participated in a JPHC Study and returned questionnaires on lifestyle and diet, including taste preferences, at both baseline and the 10th year of follow-up.

Measurements: We assessed the relations of preferences for rich and heavy taste and a sweet taste to weight changes between the age of 20 years and baseline and those during the 10-year follow-up period.

Results: Preferences for rich and heavy taste and for sweet taste were significantly positively associated with weight increases between the age of 20 years and baseline (P for trend <0.001); the fully adjusted odds ratios (95% confidence interval) comparing the 'like' versus 'dislike' groups with a preference for rich and heavy taste were 1.45 (1.31–1.24) for men and 1.28 (1.16–1.41) for women, whereas that for a sweet taste preference was 1.22 (1.09–1.36) for women. As regards weight change during the 10 years of follow-up, subjects who liked the sweet taste and those who neither liked nor disliked this taste experienced a significantly greater increase than those who disliked it in both men and women. There was no such difference for rich and heavy taste.

Conclusion: These results suggest that food taste preferences may be an important predictor of weight changes in adults. Taste preferences need to be considered when counseling patients to achieve weight control.

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Keywords: overweight; taste preference; longitudinal studies; Japan

Introduction

Obesity is known to be a risk factor for a wide range of diseases including cardiovascular disease and some cancers, and its prevention must be given high priority in modern society.¹ Energy imbalance is the most fundamental explanation for the current worldwide epidemic of obesity. Frequent intakes of energy dense foods,^{2,3} saturated fat⁴ and

sweetened beverages^{5,6} have been linked to the increasing risk of obesity, whereas greater intakes of dietary fiber,⁷ and fruits and vegetables⁸ have been shown to be protective against obesity. Food selection may be determined by various factors, including knowledge, preference and environment.⁹ Among these, taste preferences are formed in the early stage of life¹⁰ and may have a marked influence on the choice of foods throughout an individual's lifetime.¹¹ As it is difficult to estimate energy intake over a long period of time, taste preferences may provide additional information on dietary habits that cannot easily be ascertained by a standard dietary assessment.¹²

Compatible with the worldwide trend, the prevalence of obesity in Japan has also been increasing.^{13,14} Traditionally, the Japanese diet is characterized by an essentially simple

Correspondence: Dr M Noda, Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655 Japan.

E-mail: mnoda@imcj.hosp.go.jp

⁶See Appendix

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taste, with a minimum amount of oil being used in cooking, although it contains a large amount of salt.¹⁵ Owing to the westernization of lifestyles, fatty and sweetened foods have become much more readily available in Japan. In such a food environment, it may be that persons who have a preference for fatty foods or sweets have a greater risk of developing obesity or overweight than those who do not. However, there is little actual evidence linking weight change with taste preferences.¹⁶

The objective of this study was to investigate weight increases during adulthood in association with two types of taste preference: one for a rich and heavy taste, and the other for a sweet taste. These associations were examined using data from a large-scale population-based cohort study in Japan.

Subjects and methods

The JPHC Study

The data used in this study were derived from the Japan Public Health Center-based Prospective Study (JPHC Study) Cohort I, a large-scale, population-based cohort study of residents in 15 administrative areas covered by a total of five public health centers in Ninohe (Iwate prefecture), Yokote (Akita prefecture), Saku (Nagano prefecture), Ishikawa (Okinawa prefecture) and Katsushika-kita (Tokyo metropolis). These PHC areas were selected to represent the extent of variation in the mortality rate of stomach cancer based on our previous ecological study.¹⁷ Most of the centers are located in rural areas. The Japanese inhabitants were identified by the population registries maintained by the local municipalities.¹⁸ The target age of the JPHC Study Cohort I was between 40 and 59 years at the baseline survey, which was carried out mainly in 1990. A self-administered questionnaire was distributed to study participants at the baseline, 5th- and 10th-year follow-up surveys. The design of the JPHC Study has been reported in detail elsewhere.¹⁹ This study was approved by the human ethics review committees of the National Cancer Center.

Assessment of taste preference and lifestyles

Items included in the baseline questionnaire were socio-demographic factors, medical history, health-related lifestyle factors, as well as height and weight, and any increase in weight of more than 5 kg from age 20 years to baseline (yes or no). Diet was assessed by using a 44-item food frequency questionnaire, and energy intake (kcal), fat intake (g), and energy ratios of protein, fat and carbohydrate were estimated. The validation of this food frequency questionnaire was reported previously.²⁰ Taste preferences for foods were obtained by asking whether they liked the rich and heavy taste (*kotteri* in Japanese) and whether they liked the sweet taste. *Kotteri* is a word that all Japanese would know, indexing a taste as common as sweet or sour, and described as a rich and heavy taste in the *Kojien*, one of the most

popular Japanese dictionaries. The questioning sentence used was as follows: '*Kotteri to shita ryori wa suki desu ka?* (Do you like rich and heavy food?)' The possible responses to each taste preference were 'dislike', 'neither dislike nor like (hereafter 'neither')' and 'like.' At the 10-year survey, body height and weight were also self-reported. Body mass index (BMI) was calculated as weight in kilograms divided by square height in meters. Of JPHC Study participants at baseline, 5575 men and 9736 women attended health check-up and provided measured data on height and weight;¹⁷ the Spearman's correlation coefficients between BMI based on self-reported data and that on measured data were 0.89 and 0.91 for men and women, respectively.

Study subjects

Overall, a total of 50 245 residents (82%) returned the baseline questionnaire. In total, 37 860 (75%) people responded to the follow-up study conducted 10 years after the baseline. For this analysis, we excluded the 1648 subjects in the Tokyo-Katsushika public health center because individuals surveyed in these areas were limited to those aged 40 or 50 years, or were selected from among participants in a health check-up program. Furthermore, we excluded 7109 subjects who had a self-reported BMI <14 or >40 kg m⁻² or who had data missing from the baseline and/or 10-year follow-up survey. We also excluded the following subjects: those with any self-reported serious illness (cancer, cerebrovascular disease, myocardial infarction, chronic liver disease or angina pectoris) at baseline; those who did not answer baseline survey questions on taste preferences, smoking history, alcohol drinking, exercise habit, oil use and weight change from age 20 years to present and those whose energy intake was <900 or >4000 kcal for men and <800 or >3600 kcal for women. These exclusions left 29 103 subjects (13 443 men and 15 660 women) who were appropriate for the final analysis. Among subjects who had valid data on BMI and taste preference at baseline, those who remained in the analysis were slightly younger than those excluded from the analysis; mean (s.d.) age of the former and latter groups, respectively, was 49.1 (5.9) and 51.2 (5.7) years in men and 49.4 (5.8) and 50.4 (5.8) years in women. There was little difference in BMI and taste preferences between the two groups.

Analyses

All analyses were done in a sex-specific manner. We compared baseline characteristics of study subjects according to taste preferences, and their trend associations were assessed by using a linear regression analysis for continuous variables or a logistic regression analysis for categorical variables, with values of 1–3 assigned to categories of taste preference. Logistic regression analysis was used to estimate the odds ratio of having a more than 5 kg weight increase between age of 20 years and the baseline for each taste preference, using the answer 'dislike' as the reference. Two

types of adjustments were made; first, age and study area (Okinawa or other); second, age, study area, smoking (never, former or current) and exercise ($1 <$ per week or $1 \geq$ per week) at baseline. Study area was adjusted for because of a large difference in obesity levels between Okinawa and other areas.¹³ The relationships between taste preferences and changes in body weight from baseline to the 10-year survey were examined by analysis of covariance. Two types of adjustments were made; first, age, study area (Okinawa or other) and body weight at baseline; second, age, study area, body weight, smoking (never, former or current) and exercise ($1 <$ per week or $1 \geq$ per week) at baseline. Trend associations were assessed with ordinal numbers 1–3 assigned to categories of taste preference. All analyses were performed using SPSS (Version 15.0, SPSS Inc, Chicago, IL, USA).

Results

Table 1 shows the baseline characteristics of the subjects. The mean BMI increased in the order of groups responding 'dislike,' 'neither' and 'like' to the questions about taste

preferences, respectively, in both tastes. There were no differences in energy intake, protein energy ratio, fat energy ratio, carbohydrate energy ratio or exercise among the three groups for either taste. The proportion of persons with frequent consumption of oily foods increased in the order of 'dislike,' 'neither' and 'like' for the rich and heavy taste among both men and women.

Table 2 shows the odds ratio of having a more than 5 kg weight increase between age 20 years and the baseline survey for each taste preference in those answering 'dislike', as the reference group, according sex. There was a significant positive association between a preference for rich and heavy taste and the risk of weight increase for both men and women, and between preference for sweet taste and the risk only for women, with adjustment for age and study area (P for trend <0.001). The association did not fundamentally change after further adjustment for other potential confounding variables (P for trend <0.001). The fully adjusted odds ratios (95% confidence interval) comparing the 'like' versus 'dislike' groups with a preference for rich and heavy taste were 1.45 (1.31–1.61) for men and 1.28 (1.16–1.41) for women, whereas that for a sweet taste preference was 1.22

Table 1 Baseline characteristics: JPHC Study

	Men				Women			
	Dislike	Neither dislike nor like	Like	Trend P	Dislike	Neither dislike nor like	Like	Trend P
Rich and heavy taste								
No. of participants	2880	7066	3497		3638	8812	3210	
Age (years)	49.5 (5.8)	49.1 (6.0)	48.6 (5.8)		50.1 (5.7)	49.5 (5.8)	48.4 (5.8)	
People living in Okinawa (%)	13.9	23.5	29.5	<0.001	14.2	21.3	29.0	<0.001
Body height (cm)	163.8 (6.0)	164.0 (6.0)	164.5 (6.1)	<0.001	151.5 (5.2)	151.8 (5.2)	151.9 (5.2)	0.004
Body weight (kg)	61.7 (8.0)	63.4 (8.3)	65.2 (8.7)	<0.001	53.4 (7.5)	54.1 (7.2)	55.3 (7.7)	<0.001
Body mass index (kg m^{-2})	23.0 (2.6)	23.5 (2.7)	24.1 (2.8)	<0.001	23.2 (3.1)	23.5 (3.0)	24.0 (3.1)	<0.001
Current smoking (%)	53.7	49.5	52.9	0.733	5.3	3.8	5.8	0.436
Alcohol drinking (%) ^a	61.5	59.6	59.8	0.188	6.8	6.1	7.1	0.672
Exercise (%) ^b	16.2	18.3	19.0	0.006	14.5	14.7	13.2	0.134
Energy intake (kcal per day) ^c	2223 (591)	2169 (583)	2194 (602)	0.100	1436 (339)	1457 (333)	1474 (365)	<0.001
Protein energy ratio (%)	12.0 (2.1)	12.0 (2.0)	11.9 (2.1)	<0.001	14.9 (2.2)	14.8 (2.0)	14.7 (2.1)	<0.001
Fat energy ratio (%)	14.2 (4.9)	14.7 (4.8)	14.9 (4.9)	<0.001	19.6 (5.3)	20.3 (5.1)	20.5 (5.1)	<0.001
Carbohydrate energy ratio (%)	62.8 (8.9)	62.7 (8.6)	61.9 (8.8)	<0.001	63.2 (7.0)	62.7 (6.5)	62.2 (6.9)	<0.001
Fat (g)	34.2 (13.6)	34.6 (12.6)	35.3 (13.0)	0.001	31.4 (12.1)	32.9 (11.6)	33.6 (11.9)	<0.001
Oily foods (%) ^d	52.7	66.8	76.8	<0.001	59.3	72.4	79.8	<0.001
Sweet taste								
No. of participants	3304	6715	3424		1758	8069	5833	
Age (years)	48.6 (5.8)	49.1 (5.9)	49.4 (5.9)		49.6 (5.9)	49.5 (5.8)	49.1 (5.8)	
People living in Okinawa (%)	20.0	22.3	27.2	<0.001	20.5	20.1	23.0	0.001
Body height (cm)	164.3 (6.0)	164.1 (6.0)	163.9 (6.1)	0.005	151.4 (5.2)	151.7 (5.2)	151.9 (5.2)	<0.001
Body weight (kg)	63.4 (8.3)	63.5 (8.4)	63.7 (8.8)	0.227	53.3 (7.5)	53.9 (7.3)	54.8 (7.5)	<0.001
Body mass index (kg m^{-2})	23.5 (2.6)	23.6 (2.7)	23.7 (2.9)	0.001	23.3 (3.1)	23.4 (3.0)	23.7 (3.0)	<0.001
Current smoking (%)	60.7	49.9	45.0	<0.001	11.1	4.2	3.0	<0.001
Alcohol drinking (%) ^a	80.2	61.1	38.5	<0.001	15.2	6.1	4.3	<0.001
Exercise (%) ^b	17.5	18.5	17.7	0.840	15.8	15.1	13.0	<0.001
Energy intake (kcal per day) ^c	2226 (586)	2187 (586)	2149 (601)	<0.001	1464 (375)	1453 (336)	1456 (339)	0.699
Protein energy ratio (%)	11.7 (2.2)	12.0 (2.0)	12.2 (2.0)	<0.001	14.6 (2.3)	14.9 (2.1)	14.7 (2.1)	0.103
Fat energy ratio (%)	14.0 (4.8)	14.7 (4.8)	15.2 (5.0)	<0.001	19.6 (5.6)	20.3 (5.0)	20.1 (5.1)	0.038
Carbohydrate energy ratio (%)	59.3 (9.0)	62.7 (8.5)	65.3 (8.0)	<0.001	61.8 (8.0)	62.6 (6.6)	63.1 (6.5)	<0.001

Abbreviations: BMI, body mass index (kg m^{-2}). ^aAlcohol drinking: drinking more than three times per week. ^bExercise: exercising more than once a week. ^cEnergy intake from alcohol is included. ^dOily foods: consuming oily foods more than three times per week. Values except for percentages are means (s.d.).