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

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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].

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

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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.

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					
	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)
Multivariate OR ¹	1	(reference)	1.20	(1.02-1.41)	1.39	(1.16-1.67)
Multivariate OR ²	1	(reference)	1.19	(1.01-1.40)	1.36	(1.13-1.63)

p for trend

< 0.001

< 0.001

0.001

Women

	Perceived Mental Stress					
	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)
Multivariate OR ¹	1	(reference)	1.11	(0.93-1.33)	1.25	(1.01-1.56)
Multivariate OR ²	1	(reference)	1.12	(0.94-1.34)	1.22	(0.98-1.51)

p for trend

0.020

0.038

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)							
	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)
Multivariate OR ¹	1	(reference)	1.06	(0.92-1.23)	1.02	(0.85-1.21)	1.12	(0.96-1.31)
Multivariate OR ²	1	(reference)	1.06	(0.91-1.22)	1.00	(0.84-1.20)	1.09	(0.94-1.27)

p for trend

0.038

0.20

0.381

Women

	Levels of Type A behavior pattern (4 = most Type B, 1 = most Type A)							
	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)
Multivariate OR ¹	1	(reference)	0.93	(0.80-1.09)	1.05	(0.86-1.27)	1.25	(1.03-1.50)
Multivariate OR ²	1	(reference)	0.93	(0.79-1.09)	1.03	(0.85-1.26)	1.22	(1.01-1.47)

p for trend

0.044

0.014

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 ≥ 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 ≥ 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 ≥ 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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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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