2型糖尿病発症に関わる危険因子のリスク

（多重ロジスティック回帰）

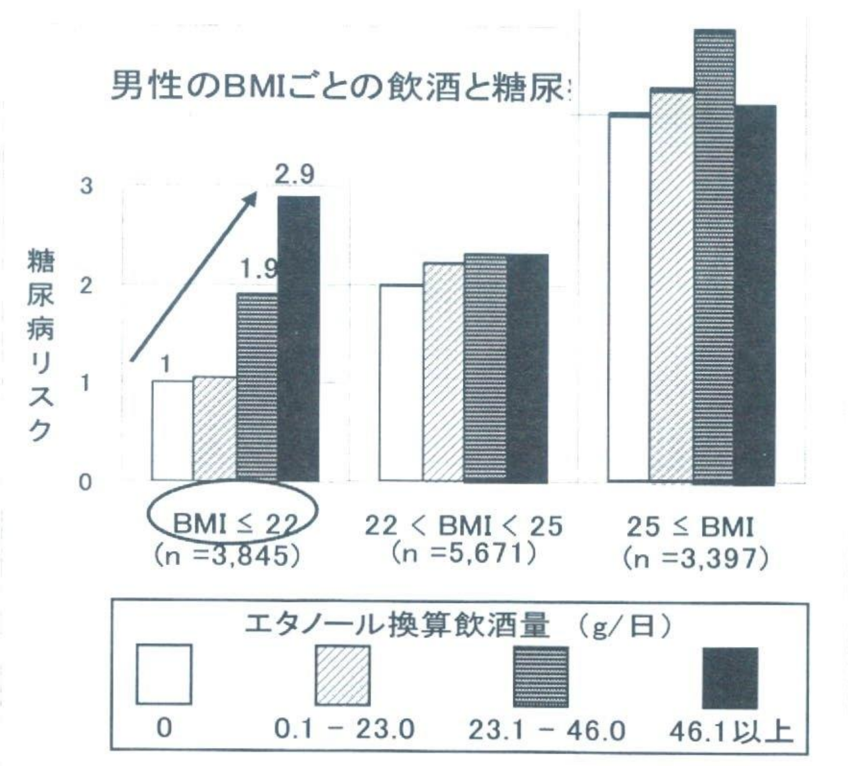
男　性

（n=12,913）

		オッズ比	(95% CI)
アルコール	非飲酒	1.00	(referent)
	0g＜エタノール≦23.0g	1.08	(0.87-1.34)
	23.0g＜エタノール≦46.0g	1.26	(1.02-1.56)
	エタノール＞46.0g	1.25	(1.00-1.56)

傾向性検定
P=0.019

Waki K, Noda M, et al: ***Diabetic Med 21****: 323-331, 2005*



Waki K, Noda M, et al: ***Diabetic Med 21****: 323-331, 2005*

2型糖尿病発症に関わる危険因子のリスク

（多重ロジスティック回帰）

女　性

（n=15,980）

	オッズ比 (95% CI)	
年齢 (1歳あたり)	1.02	(1.01-1.04)
BMI (1 kg/m^2あたり)	1.17	(1.14-1.21)
家族歴 (あり/なし)	2.69	(2.12-3.43)
運動習慣(あり/なし)	1.06	(0.82-1.37)
高血圧の既往(あり/なし)	1.79	(1.44-2.22)

*Waki K, Noda M, et al: **Diabetic Med 21**: 323-331, 2005*

2型糖尿病発症に関わる危険因子のリスク

女　性　（多重ロジスティック回帰）

（n=15,980）

		オッズ比 (95% CI)	
喫煙	非喫煙	1.00	(referent)
	現在の喫煙:		
	1-19 本/日	1.07	(0.62-1.86)
	≧20 本/日	2.94	(1.57-5.50)
	過去の喫煙	2.77	(1.67-4.61)
アルコール	非飲酒	1.00	(referent)
	0g＜エタノール≦4.9g	1.15	(0.68-1.95)
	4.9g＜エタノール≦11.5g	0.81	(0.48-1.35)
	エタノール＞11.5g	0.78	(0.44-1.40)

*Waki K. Noda M. et al: **Diabetic Med 21**: 323-331. 2005*

まとめ-１．厚労省多目的コホート調査の解析

自己申告糖尿病の前向きコホート解析

1. これから、一般の日本人（中年一般住民）における糖尿病の発症年率は、男性 1.12%、女性 0.60%と推定された。（中年一般住民における10年間の自己申告による糖尿病の発症率は男性5.4%、女性3.0%であった。）
2. 年齢、BMI、糖尿病の家族歴、高血圧、過去の喫煙および現在20本以上の喫煙は男女とも糖尿病発症のリスクを有意に上昇させていた。男性ではBMI22以下の群において一日のエタノール摂取量＞23g（日本酒換算で1合）の者では、糖尿病発症のリスクが有意に上昇した。
3. 禁煙により糖尿病発症のリスクは有意に減少した。

精神的ストレス、コーヒー摂取と糖尿病発症との関連

ストレスによる糖尿病発症のリスク変化

日常、あなたの受けるストレスは多いと思われますか？

少ない、ふつう、多い

「少ない」を reference として

男性*

「ふつう」	OR=1.16	(95%CI 0.88～1.54)
「多い」	OR=1.54	(95%CI 1.14～2.07)

女性

「ふつう」	OR=1.23	(95%CI 0.91～1.67)
「多い」	OR=1.34	(95%CI 0.98～1.95)

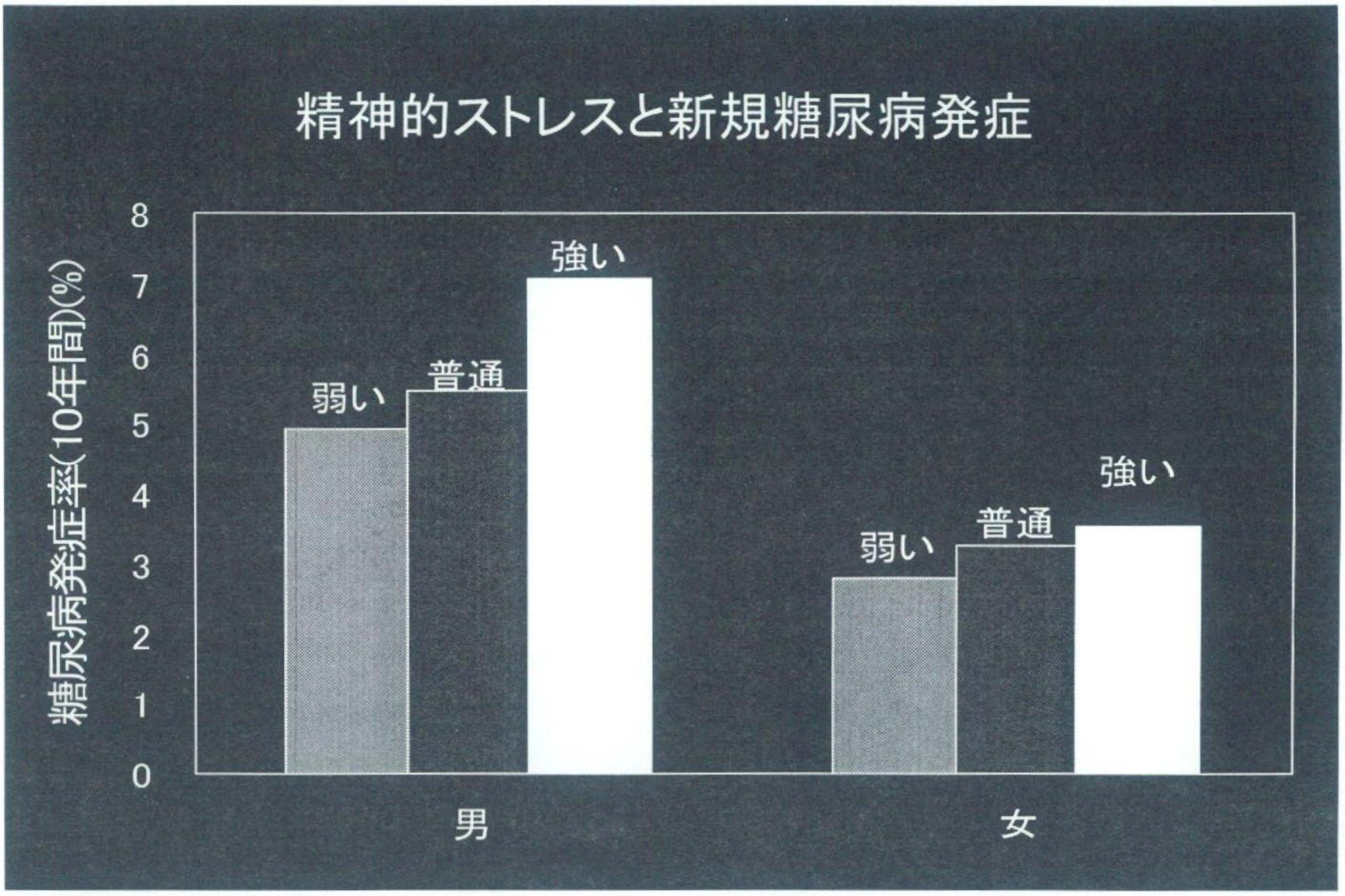
年齢、BMI、喫煙、アルコール摂取、糖尿病の家族歴、運動習慣、高血圧の既往で調整

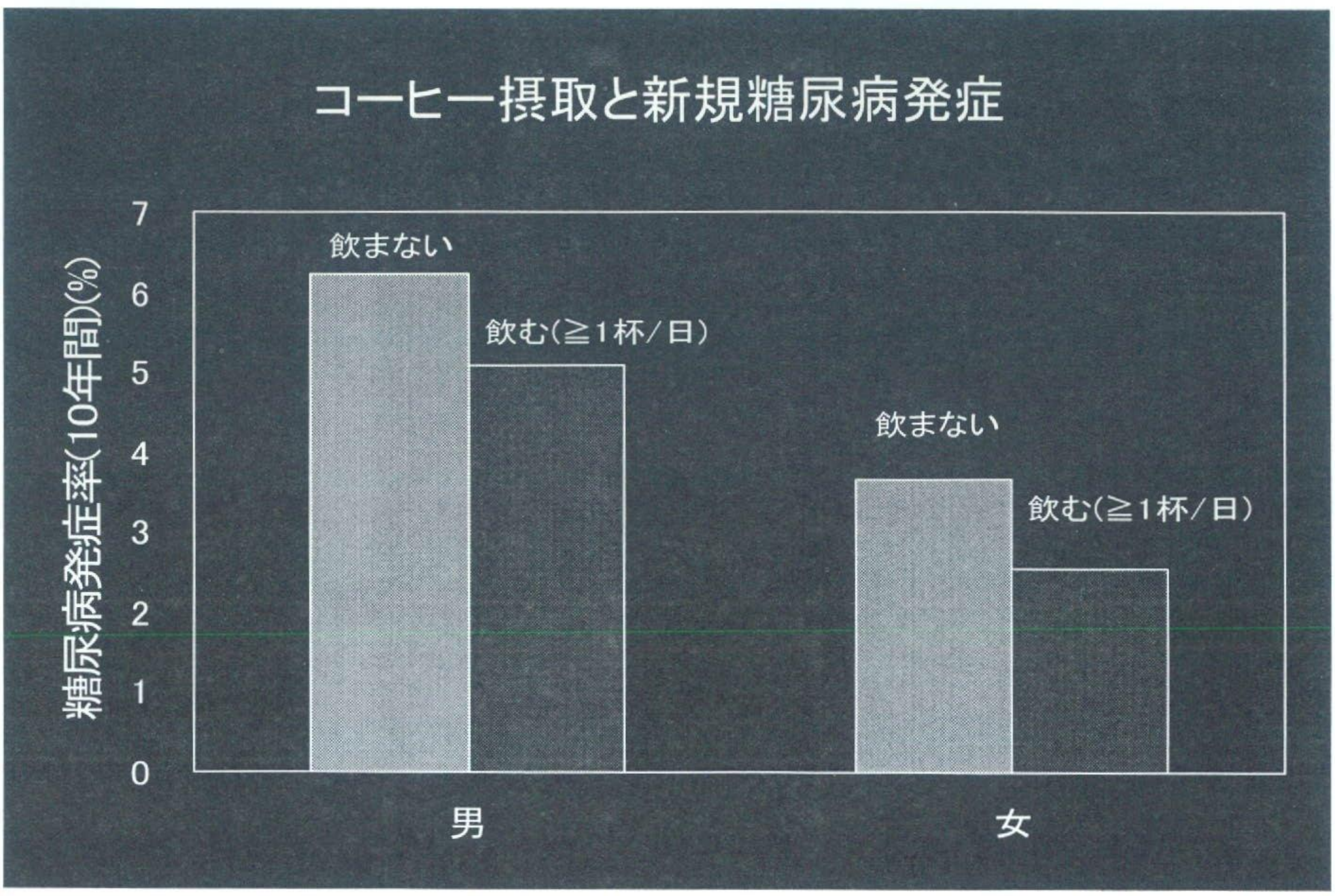
*とくに横手で有意性が強かった。

【目的】コホートのデータに基づき、糖尿病発症および関連する要因を調べる

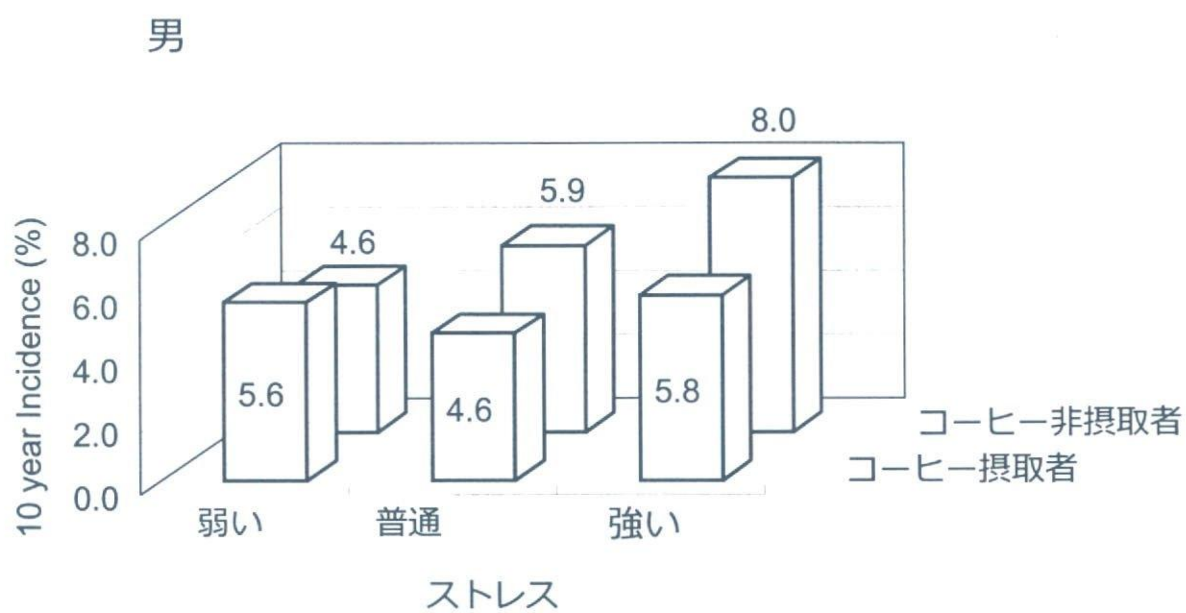
【対象者】 コホートⅠ(二戸、横手、佐久、沖縄石川)
1990年(ベースライン)～1999年(10年後調査)

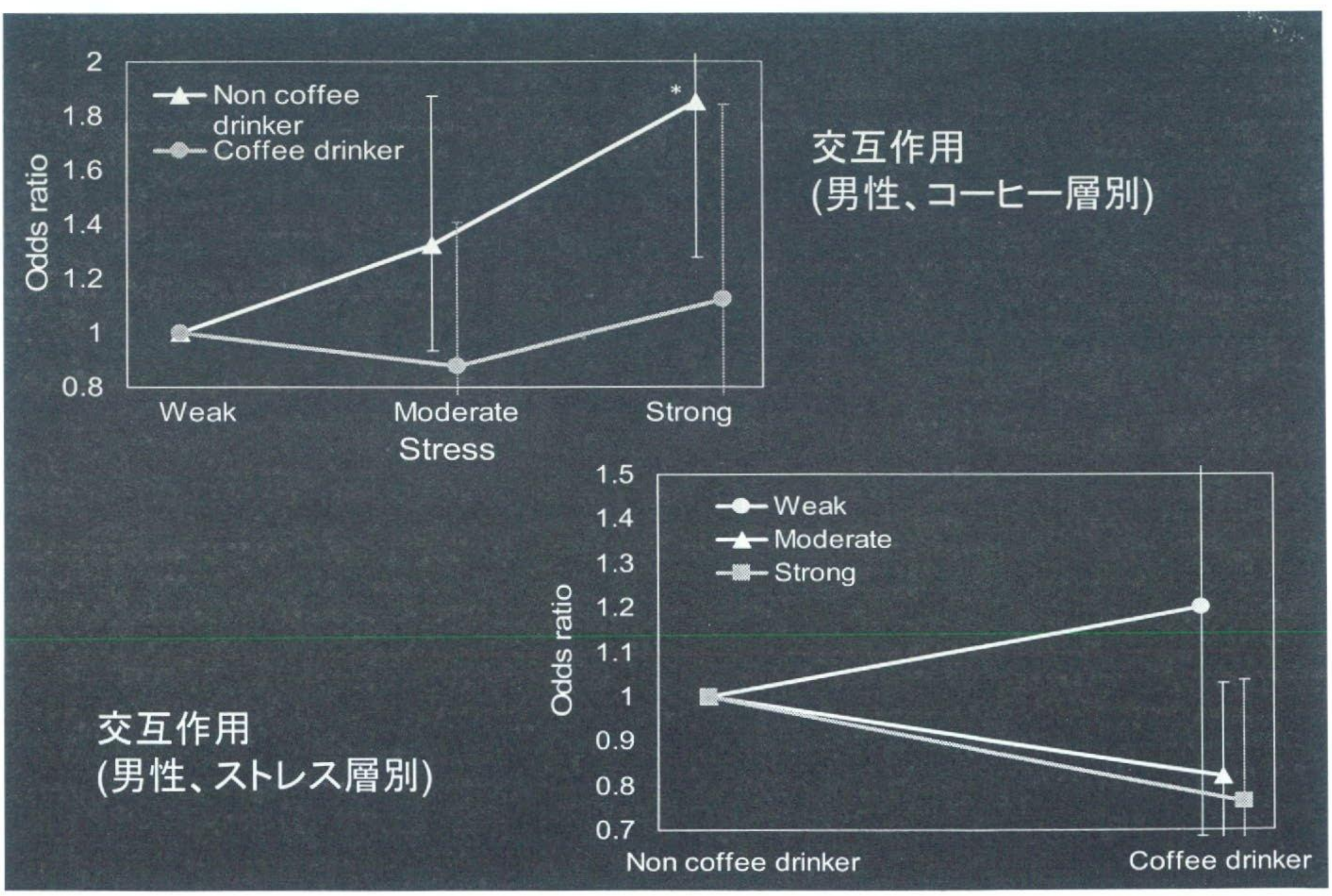
【糖尿病発症】自己申告による(診断または治療)。
ベースラインで糖尿病でない対象者を１０年間追跡。５年後、１０年後調査いずれかで糖尿病の場合に糖尿病発症とした。


精神的ストレスと新規糖尿病発症
糖尿病発症率(10年間)(%)
8
7
6
5
4
3
2
1
0
弱い
普通
強い
男
弱い
普通
強い
女


コーヒー摂取と新規糖尿病発症
糖尿病発症率(10年間)(%)
7
6
5
4
3
2
1
0
飲まない
飲む(≧1杯/日)
男
飲まない
飲む(≧1杯/日)
女

コーヒーとストレスの相互作用





精神的ストレスと糖尿病との関連

1. 横断研究ではこれまでいくつか報告あり。
2. コホート研究では、航空管制官(Cobbら, 1973)、残業や新しい技術が必要な仕事(Kawakamiら, 1999)で糖尿病発症増加との報告があるが、対象が特殊であり、またはっきりとした結果ではない。
3. 生物学的にはHPA系、コルチゾールや交感神経系、IL-6などと関連？

まとめ-2

1. 最近報告されているコーヒー摂取の糖尿病発症に対する相関を確認した。
2. 精神的ストレスが糖尿病発症の有意に相関することを示した。(大規模な一般の集団でははじめて)
3. コーヒーとストレスとの間に交互作用の可能性を示した。

厚労省多目的コホート調査の解析

同調査で確認された生活習慣と、健診時空腹時高血糖や自己申告による糖尿病との関係の解析

1．自己申告糖尿病の前向きコホート解析

2．健診時空腹時高血糖の横断解析

方法

健診で空腹時採血の多かった葛飾コホートにおいて、空腹時高血糖の有無、空腹時血糖値と生活習慣との関係を分析

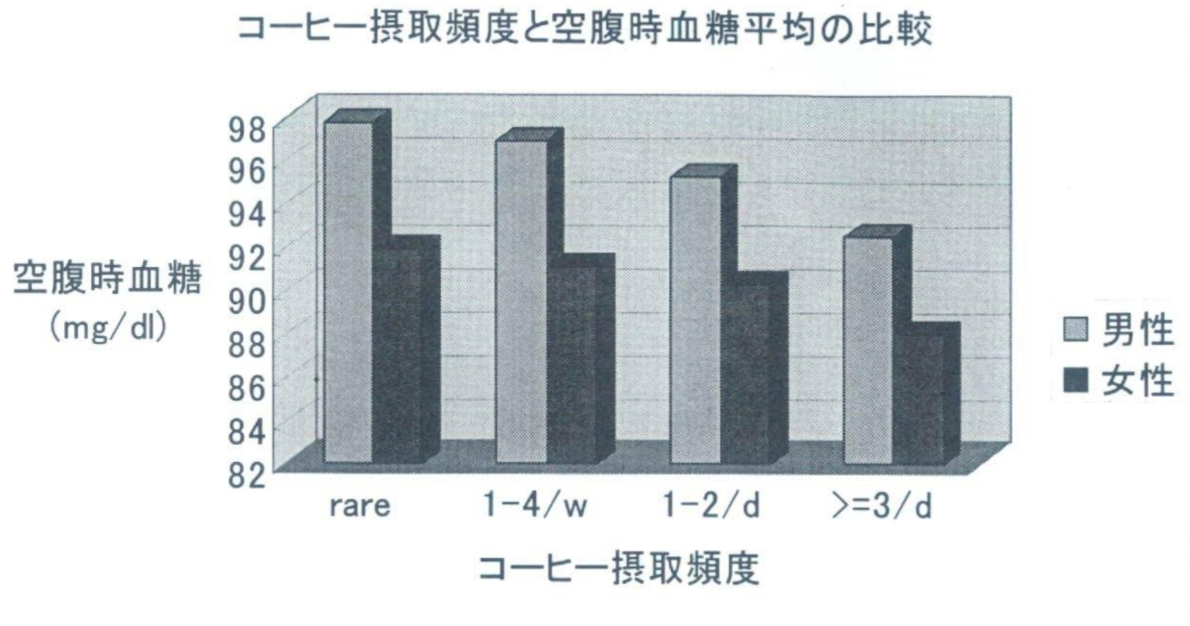
対象

厚労省コホートのベースライン質問票に答えた対象者のうち朝食前採血を行った男性1911人、女性2691人（虚血性心疾患、肝疾患などを有する者を除いた）

解析

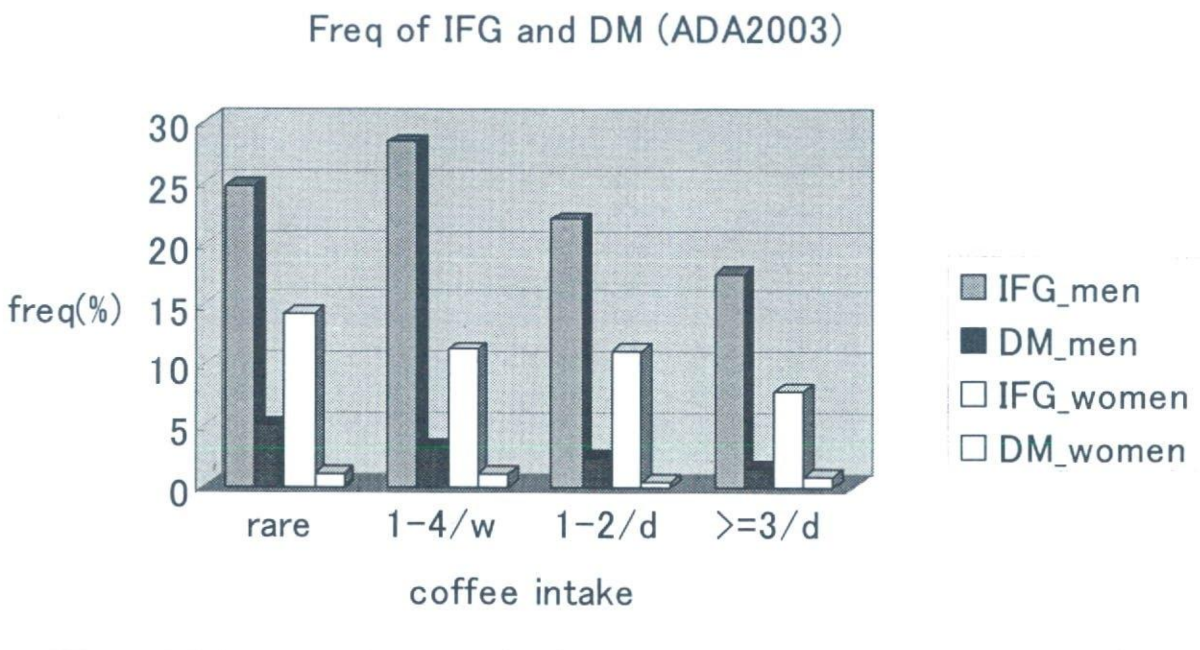
Multivariate logistic regression analysis

コーヒー摂取と空腹時血糖値との関係
（葛飾コホート）



コーヒー摂取と空腹時で見た血糖値の型判定との関係
（葛飾コホート）

IFG: impaired fasting glucose, DM: diabetes mellitus



今後の計画

1. ほぼ終了した２回目の糖尿病調査（2003-5年度）の結果とから、検査データによって把握された糖尿病の確実な新規発症を対象に、その発症と生活習慣等との関係を分析する。
2. 厚生労働省多目的コホート班のベースライン調査、５年後、10年後調査のデータを用いた自己申告による糖尿病発症因子に関する解析をさらに進める。
3. 虚血性心疾患、脳血管疾患、がんなど各種疾患の発症を追跡調査し、糖尿病罹病との関係を明らかにする。

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ご静聴ありがとうございました

DME

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Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I

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Accepted 15 March 2004

Abstract

Aims Few prospective studies have examined the relationship between lifestyle characteristics and the incidence of diabetes mellitus in an Asian general population. This study was undertaken to evaluate the risk factors for Type 2 diabetes in a population-based prospective study of middle-aged Japanese.

Methods We investigated 12 913 men and 15 980 women, aged 40–59 years at baseline (year 0), who participated in the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I. The participants were followed for up to 10 years. Incident cases of diabetes were identified by self-reporting of a physician's diagnosis on two questionnaires sent to each participant, one at year 5 and the second at year 10.

Results During the 10-year follow-up, 703 men and 482 women reported newly diagnosed diabetes. Age, body mass index (BMI), family history of diabetes and cigarette smoking were independent risk factors in both genders by multivariate analysis. Among men with a BMI ≤ 22 kg/m^2, a significant positive association was observed between the diabetes incidence and moderate (23.0 < 46.0 g/day) to high (> 46.0 g/day) alcohol consumption, odds ratio 1.91 (95% CI, 1.05–3.46) and 2.89 (1.63–5.11), respectively. Among men with a BMI > 22 kg/m^2, a small non-significant increase in odds ratio was observed with alcohol consumption.

Conclusions Established risk factors for diabetes in western populations were also identified as predictors of the disease among Japanese. Moderate to high alcohol consumption was positively associated with the incidence of diabetes in Japanese lean (BMI ≤ 22 kg/m^2) men.

Diabet. Med. 22, 323–331 (2005)

Keywords diabetes mellitus, prospective study, risk factor

Abbreviations BMI, body mass index; CI, confidence interval; JPHC, Japan Public Health Center-based prospective study on cancer and cardiovascular diseases; OR, odds ratio; PHC, public health centre

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Introduction

Type 2 diabetes is associated with a genetic predisposition [1], but is also strongly influenced by lifestyle-related factors, such as eating habits and/or physical activity [2,3]. Japanese immigrants residing in the United States and Brazil, with a westernised lifestyle but a genetic background such as siblings in their homeland, have a higher prevalence of diabetes than Japanese people living in the Far East [4–7].

However, the situation may now have changed. The prevalence of diabetes has increased dramatically in many Asian nations over the past decades [8], including Japan, possibly because of changes from a traditional to a westernised lifestyle. Prevention of diabetes through suitable lifestyle modifications is an urgent health issue in this area of the world. Thus, it is important to evaluate the risk factors for diabetes in Asian general populations to determine whether the risk factors established in western populations [2,3] also apply to Asian ethnic groups. This will help to determine whether the strategies that have proven effective in Western countries can be applied to Asians. Few published studies have attempted to answer this question by a direct comparison of the influence of lifestyles on the future development of diabetes. Some have been cross-sectional [9,10] or, despite being longitudinal, were conducted in subjects who did not represent the general population [11–16]; others were too short to be reliable [17].

To quantify the risk factors for diabetes in a general Japanese population, we conducted a community-based, prospective cohort study on a relatively large number of middle-aged adults with an adequate follow-up period.

Patients and methods

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) is an ongoing, longitudinal cohort study, investigating cancer, cardiovascular diseases and other lifestyle-related diseases. The total cohort has been divided into two, Cohort I and Cohort II [18], and the current study was conducted within the population-based part of Cohort I (the other smaller part consists of health check-up examinees), namely those residents who registered their address in one of 14 administrative districts supervised by four public health centres: the city of Ninohe and the town of Karumai in the Ninohe Public Health Center (PHC) area of Iwate Prefecture, the city of Yokote and the town of Omonogawa in the Yokote PHC area of Akita Prefecture, eight districts in Minami-Saku County in the Saku PHC area of Nagano Prefecture, and the city of Gushikawa and village of Onna in the Ishikawa PHC area of Okinawa Prefecture. The criteria for selecting the areas, subjects, and the methods of data collection have been reported previously [18,19]. This study was approved by the institutional review board of the National Cancer Center of Japan.

Participants

Briefly, 43 149 individuals (20 665 men and 22 484 women), aged 40–59 years at baseline, completed the baseline questionnaire upon enrolment in 1990 (year 0; response rates: 76% for men and 82% for women). Follow-up questionnaires were sent to each individual at years 5 and 10, and a total of 32 126 individuals (14 551 men and 17 575 women) returned both follow-up questionnaires (total follow-up rate: 74.5%; 70.4% for men and 78.2% for women). To construct the cohort for the current analysis, we excluded individuals who had any of the following conditions at baseline: diabetes (n = 1120; 742 men and 378 women), cardiovascular disease (n = 470; 257 men and 213 women), chronic liver disease (n = 311; 215 men and 96 women), kidney disease (n = 546; 214 men and 332 women) or cancer (n = 689; 205 men and 484 women). Individuals who had missing baseline data for any of the exposure parameters described below were also excluded (n = 298; 121 men and 177 women). After these exclusions, the remaining cohort consisted of 28 893 participants (12 913 men and 15 980 women) with data on incident diabetes.

Data collection

Each participant completed a self-administered questionnaire that included questions regarding weight and height, usual pattern of physical activity, smoking habits, alcohol intake, previously diagnosed medical conditions (including diabetes and hypertension), family history of diabetes, use of drugs, and other lifestyle factors. Subjects were classified according to smoking habit as 'never smoked', 'former smokers', and 'current smokers'; the last group was subdivided into two groups according to the number of cigarettes smoked daily: 1–19 or ≥ 20 cigarettes/day. Questions on alcohol intake included items about the types of alcoholic beverages consumed, the frequency of alcohol consumption (per week), and the usual amount of alcohol consumed daily. Total daily alcohol intake was calculated by multiplying the frequency of consumption by the alcohol content of the beverage: 23 g ethanol per 180 ml of Japanese sake (rice wine), 36 g ethanol per 180 ml of shochu or awamori (both Japanese distilled liquors), 10 g ethanol per 30 ml of whisky or brandy, 6 g ethanol per 60 ml of wine and 23 g ethanol per 633 ml of beer. According to their current drinking behaviour, the subjects were classified into two groups: 'non-drinkers and infrequent occasional drinkers (who consume alcohol on three or fewer days per month)' and 'drinkers'. The 'drinkers' category was further subdivided by the tertiles of daily ethanol consumption. We previously reported that this questionnaire was found to measure average alcohol consumption with a high degree of validity [19]. Physical activity was assessed using the replies to questions regarding the number of times per week or month that the subject engaged in sports activities during leisure time. Subjects were considered physically active if they participated in sports at least once a week; all other subjects were considered inactive. A history of hypertension was considered to exist if the subject had been informed of a diagnosis of hypertension by a doctor and/or was receiving a prescription for anti-hypertensive drug(s). The prevalence of hypertension as documented using the self-administered questionnaire was verified in a subpopulation of the cohort for whom health check-up data were available. In this subpopulation, documented hypertension was confirmed in 90.2% (1989/2204) of the subjects, i.e. those 1989 subjects fulfilled at least one of the following criteria: (i) systolic blood pressure ≥ 140 mmHg, (ii) diastolic blood pressure ≥ 90 mmHg or (iii) being prescribed anti-hypertensive drug(s). Among the 13 321 subjects without self-report-documented hypertension, 3097 had hypertension, i.e. fulfilled criterion (i) and/or (ii) and/or (iii). A subject's family history of diabetes was considered positive if at least one parent or one sibling had diabetes. Body mass index (BMI) was calculated as the weight (kg)/[height (m)]^2 and used as an index of relative weight. The subjects' weight and height acquired from the questionnaire were validated by the data obtained from the health check-up, which about one-third of the subjects voluntarily underwent [20].

Ascertainment of diabetes mellitus

Whether the subject had a prevalent disease was determined by the questions on the baseline questionnaire: i.e. 'Has a doctor ever told you that you have any of the following diseases?—diabetes (yes/no), hypertension (yes/no)', and so forth. 'Prevalent diabetes' was defined as a reply of 'yes' to the question concerning diabetes. Individuals with diabetes at baseline were excluded from this analysis. Individuals without diabetes at baseline who subsequently answered 'yes' on either or both of the follow-up questionnaires at years 5 and 10 were considered to have developed diabetes. A total of 1183 subjects (703 men and 480 women) reported the development of diabetes during the 10-year study period. We classified all incident cases of diabetes as Type 2, as the age of onset in this middle-aged cohort was 40 years or older.

To document the validity of the self-report, we examined a series of medical records as follows. For practical reasons, three of the 14 administrative districts were chosen to validate the questionnaire information. In these areas, there were 207 participants recorded as having diabetes at year 5. We sent a letter to these participants requesting permission to examine their medical records and 167 replies were received. Of these, 154 participants were confirmed as having diabetes again by self-report. Permission to review their medical records was obtained from 110 of the 154 participants, and the records of 93 participants (54 men and 39 women) of major hospitals were chosen for verification. Two specialists in diabetes (M.N. and Y.T.) reviewed the records, and diabetes was confirmed if any of the following criteria were met: (i) the World Health Organization (1985) criteria [21], (ii) a high casual plasma glucose level (≥ 11 mmol/l), or (iii) use of diabetic medication (insulin or oral hypoglycaemic agent). Thirty subjects (19 men and 11 women) met criterion (i), eight subjects (five men and three women) met criterion (ii), and 38 subjects (20 men and 18 women) met criterion (iii). When we applied the new criteria of the American Diabetes Association (1997) [22], the number of confirmed cases of diabetes did not change, as none of the subjects with a 2-h post-challenge level of < 11 mmol/l had a fasting plasma glucose level in the diabetic range specified by the new criteria alone. In summary, a diagnosis of diabetes was confirmed in a total of 76 of the 93 subjects (82%) who were screened, which we considered reasonable and sufficiently high for a large-scale study. Among the 17 subjects in whom a diagnosis of diabetes was not confirmed, the medical records of 12 subjects were unavailable ($n = 9$) or contained insufficient data to justify a diagnosis of diabetes ($n = 3$). When only subjects for whom complete medical records were available were analysed, the percentage of confirmed diagnosis increased to 94%.

We also conducted a cross-sectional survey to examine whether self-report of diabetes agreed with diagnosis based on health check-up data among Cohort I participants. We collected blood samples from 12 460 subjects (29% of the study cohort) who voluntarily participated in the health check-up examination. Participants were determined to have diabetic hyperglycaemia based on their health check-up data if at least one of the following criteria was met: (i) fasting plasma glucose ≥ 7 mmol/l, (ii) casual plasma glucose ≥ 11 mmol/l, or (iii) HbA_{1c} ≥ 6.1% [23]. In a preliminary analysis, out of 1075 subjects with diabetic hyperglycaemia, 498 reported diabetes; meanwhile, among 11 385 subjects without diabetic hyperglycaemia, 11 169 did not report diabetes. According to these results, the sensitivity and specificity of the questionnaire for diabetic hyperglycaemia was roughly 46% and 98%, respectively. Although these analyses were performed without regard to the self-reported current treatment for diabetes, the number of subjects with a self-report of pharmacological treatment without diabetic hyperglycaemia was very small (~0.4% of the total number of subjects who were without diabetic hyperglycaemia); therefore, overestimation of specificity by this was likely to be within a negligible range.

Analysis

All analyses were performed separately for men and women. The statistical significance of baseline differences with regard to diabetes status at follow-up in relation to established and suspected risk factors for Type 2 diabetes was assessed using *t*-tests and χ^2-tests. A P-value < 0.05 was considered significant. The cumulative incidence of diabetes over the 10-year period was selected as the outcome, (a) because risk estimates could be calculated directly, and (b) because the lack of precise dates of diabetes onset precluded the use of a person-year approach. 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. Multiple logistic regression analysis was used to assess the independent contributions of the risk factors to the subsequent risk for Type 2 diabetes and to obtain odds ratios that were adjusted for the other risk factors. Smoking status (four levels), alcohol intake [four levels, ALC_0 consists of non-drinkers (1349 men and 1916 women) and infrequent occasional drinkers who consume alcohol on three or fewer days a month (2449 men and 12 331 women)], physical exercise (active/inactive), family history of diabetes (positive/negative), and prevalent hypertension (positive/negative) were fitted as categorical variables in our logistic model. Because there were no significant interactions between any of the variables and the areas where the subjects resided, the geographical areas were not included as a variable in the final model and all four areas were analysed together. The 95% confidence interval for each odds ratio was calculated. The Mantel extension test was employed to analyse the trend across increasing levels of alcohol consumption. Statistical significance was determined by 95% confidence intervals not including 1.00 for logistic analyses. The statistical analyses were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

To examine the possible existence of a significant interaction between alcohol consumption and BMI with regard to the risk of diabetes, we conducted a stratified analysis for BMI with cut-off levels set at 22 and 25 kg/m^2; these values represent the ideal BMI and the lower BMI limit of obesity, respectively, for Japanese people as defined by the Japan Society for the Study of Obesity [24]. The former value was determined by the BMI associated with the lowest level of morbidity among middle-aged Japanese [25].

Results

Incident Type 2 diabetes mellitus (Table 1)

During the 10-year follow-up, we documented 703 incident cases (5.4%) of diabetes among men and 480 cases (3.0%) among women. There was male predominance in the incidence of diabetes.

Risk factors for diabetes at baseline (Table 2)

Subjects of both genders who converted to a diabetes-positive status were significantly older and had a higher BMI than those who remained non-diabetic. In addition, higher percentages of subjects were positive for smoking, family history of diabetes and past history of hypertension among those who became diabetic during the follow-up period than among those who remained non-diabetic. The percentage of men with moderate (ethanol intake: > 23 g/day and ≤ 46 g/day) or high (ethanol intake > 46 g/day) alcohol consumption was also higher among subjects who became diabetic during the follow-up compared with those who remained non-diabetic. There was an increasing trend for developing diabetes during the follow-up period according to alcohol consumption, and this positive trend was significant (*P* for trend = 0.007) by the Mantel extension test.

Table 1 Ten-year incidence of Type 2 diabetes mellitus in the JPHC Cohort according to gender

Age (years)	Men		Women	
40–49	309/6404	(4.8)	191/7698	(2.5)
	80/1471	(5.4)	52/1951	(2.7)
	80/1835	(4.4)	47/2230	(2.1)
	90/1900	(4.7)	47/2069	(2.3)
	59/1198	(4.9)	45/1448	(3.1)
50–59	394/6509	(6.1)	289/8282	(3.5)
	92/1386	(6.6)	71/1939	(3.7)
	98/1889	(5.2)	91/2650	(3.4)
	118/1955	(6.0)	81/2251	(3.6)
	86/1279	(6.7)	46/1442	(3.2)
Total	703/12 913	(5.4)	480/15 980	(3.0)

Data are incidence/total number and the per cent (in parentheses). Below the total number and per cent, incidence of diabetes and the per cent of each subcohort are shown. The data are shown for (top to bottom) the Ninohe PHC area of Iwate Prefecture, the Yokote PHC area of Akita Prefecture, the Saku PHC area of Nagano Prefecture, and the Ishikawa PHC area of Okinawa Prefecture.

BMI, family history of diabetes, smoking and risk of diabetes (Table 3)

Multiple logistic regression analysis was performed to determine which of the baseline characteristics that had been previously identified as risk factors in some of the earlier studies were independent predictors of diabetes in the present cohort. Age, BMI, a positive family history of diabetes and a past history of hypertension were strong predictors for the development of diabetes in both genders. Smoking status was also strongly associated with the development of future diabetes among former smokers and those smoking 20 cigarettes or more a day in both genders.

Alcohol consumption and risk of diabetes

Among men, daily alcohol consumption of 23 g of ethanol or more was significantly related to the future development of diabetes when compared with the group of non-drinkers and infrequent occasional drinkers; a positive trend across the increasing levels of alcohol consumption was also significant (*P* for trend = 0.019) according to the Mantel extension test (Table 3).

To determine whether the BMI modified the association between daily alcohol consumption and the risk of Type 2 diabetes, we stratified the subjects according to the BMI (see Table 4). Among lean men (BMI ≤ 22 kg/m^2), a significant and strong positive association with moderate to high alcohol consumption was observed and the positive trend across the increasing levels of alcohol consumption was also significant (*P* for trend < 0.001). The risk for heavy alcohol drinkers was 2.89 (95% CI, 1.63–5.11) times higher than that of non-drinkers and infrequent occasional drinkers. By contrast, among men with a BMI > 22 kg/m^2, only a small, non-significant increase was observed among alcohol consumers (Table 4). In addition, when we analysed non-drinkers and infrequent occasional drinkers separately in the analysis shown in Table 3 (i.e. without subdividing the subjects according to their BMI), the odds between these two groups were almost equal [odds ratio for the former to the latter: 1.01 (95% CI, 0.74–1.38)], with the significantly increased odds ratios for high (> 46 g/day) alcohol consumption compared with non- or occasional infrequent drinkers persisted in the lower (≤ 22 kg/m^2) BMI group, even in this stratified analysis (data not shown).

No significant association between alcohol intake and the future development of diabetes was observed among women.

Discussion

This study is the largest community-based prospective study in Japan with a 10-year follow-up period to quantify the risk factors for Type 2 diabetes. We identified established risk factors, such as age, BMI and family history of diabetes, as independent determinants of Type 2 diabetes in both men and women, consistent with the results of studies in western populations [26–34].

Table 2 Baseline characteristics and development of Type 2 diabetes mellitus in middle-aged Japanese men and women

	Men			Women		
Characteristics	Remained non-diabetic	Developed diabetes	*P*	Remained non-diabetic	Developed diabetes	*P*
Age (years)	49.4	50.1	0.002	49.6	50.8	< 0.001
	49.0, 49.5	49.8, 50.0		49.3, 49.9	50.3, 51.5	
	49.5, 49.4	50.1, 50.5		49.7, 49.2	51.3, 49.9	
BMI (kg/m^2)	23.4	25.0	< 0.001	23.5	25.6	< 0.001
	23.5, 23.2	25.2, 24.8		23.6, 23.2	25.6, 25.1	
	23.1, 24.4	24.4, 25.9		23.1, 24.2	25.2, 26.7	
Smoking status (%)			0.012			< 0.001
Never smokers	25.2	21.3		94.6	90.8	
	27.8, 23.2	25.0, 22.5		95.6, 96.0	93.5, 93.5	
	21.3, 31.5	15.4, 24.1		92.7, 93.6	92.2, 81.3	
Current smokers:						
1–19 cigarettes/day	15.2	13.2		3.1	2.9	
	16.7, 15.9	15.7, 10.7		2.8, 2.3	0.8, 2.9	
	15.6, 11.9	14.4, 11.7		4.5, 2.9	3.9, 4.4	
≥ 20 cigarettes/day	36.7	38.7		1.0	2.5	
	38.6, 38.3	41.3, 39.3		0.7, 0.8	1.6, 1.5	
	38.8, 29.2	39.9, 33.1		1.1, 1.6	0.8, 7.7	
Past smokers	22.8	26.7		1.3	3.8	
	17.0, 22.6	18.0, 27.5		1.0, 0.9	4.1, 2.2	
	24.3, 27.4	30.3, 31.0		1.7, 1.9	3.1, 6.6	
Alcohol intake* (%)			0.046			0.824
ALC_0	31.4	27.9		89.8	90.8	
	34.8, 21.8	29.7, 14.0		91.9, 87.2	93.5, 88.4	
	28.0, 47.2	22.6, 50.3		87.0, 95.7	87.5, 95.6	
ALC_1	25.9	24.0		3.0	3.1	
	23.4, 24.6	25.0, 20.8		2.2, 3.7	1.6, 3.6	
	28.7, 26.4	25.0, 25.5		4.4, 0.9	5.5, 1.1	
ALC_2	22.4	24.8		4.1	3.3	
	20.5, 27.6	21.5, 34.8		3.3, 5.1	2.4, 4.4	
	25.2, 12.4	27.4, 12.4		5.1, 1.8	3.9, 2.2	
ALC_3	20.3	23.3		3.1	2.7	
	21.3, 26.1	23.8, 30.3		2.6, 3.9	2.4, 3.6	
	18.1, 14.0	25.0, 11.7		3.6, 1.6	3.1, 1.1	
Leisure-time physical activity at least once a week (%)	17.2	16.4	0.588	14.2	15.2	0.528
	11.7, 15.4	13.6, 17.4		8.0, 11.8	11.4, 12.3	
	19.4, 22.6	13.0, 22.8		20.4, 17.3	19.5, 18.7	
Family history of diabetes (%)	8.2	15.1	< 0.001	8.1	18.8	< 0.001
	10.4, 8.6	18.6, 12.4		8.7, 8.4	25.2, 16.7	
	8.2, 5.0	17.3, 11.0		8.9, 5.9	21.1, 9.9	
History of hypertension (%)	15.0	22.5	< 0.001	13.9	29.0	< 0.001
	15.7, 18.1	26.7, 26.4		15.1, 15.3	34.2. 31.2	
	13.6, 11.6	20.2, 15.9		13.1, 11.5	23.4, 26.4	

Data are means (age and BMI) or percentages (all others).

*Alcohol intake (g/day of ethanol): men, ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0; women, ALC_1: 0 < ethanol ≤ 4.9, ALC_2: 4.9 < ethanol ≤ 11.5, ALC_3: ethanol > 11.5. ALC_0: non-drinkers and infrequent occasional drinkers who consume alcohol on three or fewer days a month.

The total data and data for each subcohort are shown. Data are shown for (left to right, top to bottom) the Ninohe PHC area of Iwate Prefecture, the Yokote PHC area of Akita Prefecture, the Saku PHC area of Nagano Prefecture, and the Ishikawa PHC area of Okinawa Prefecture.

The analysis revealed a significant positive association between moderate to high alcohol intake and future diabetes in lean men (BMI ≤ 22 kg/m^2) and a similar but non-significant correlation in obese men (BMI > 22 kg/m^2). This contrasts with the results for men in most previous studies in the United States and Europe conducted using a prospective design, which reported an inverse correlation between alcohol intake and Type 2 diabetes [33,35,36] or suggested no significant association with diabetes [37–39]. A few, however, showed an excess diabetes incidence only in heavy drinkers [40,41].

The results of the Osaka Health Survey of Japanese male employees [15] showed moderate alcohol consumption (21.1–

Table 3 Multivariate logistic regression analysis of the 10-year incidence of Type 2 diabetes mellitus in middle-aged Japanese according to gender

	Men (n = 12 913)		Women (n = 15 980)	
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Age (1-year increase)	1.02	(1.01–1.04)	1.02	(1.01–1.04)
BMI (1 kg/m²-increase)	1.17	(1.14–1.20)	1.17	(1.14–1.21)
Smoking status				
Never smokers	1.00 (referent)		1.00 (referent)	
Current smokers:				
1–19 cigarettes/day	1.14	(0.87–1.50)	1.07	(0.62–1.86)
≥ 20 cigarettes/day	1.37	(1.11–1.69)	2.94	(1.57–5.50)
Past smokers	1.35	(1.08–1.69)	2.77	(1.67–4.61)
Alcohol intake*				
ALC_0	1.00 (referent)		1.00 (referent)	
ALC_1	1.08	(0.87–1.34)	1.15	(0.68–1.95)
ALC_2	1.26	(1.02–1.56)	0.81	(0.48–1.35)
ALC_3	1.25	(1.00–1.56)	0.78	(0.44–1.40)
Family history (yes/no)	2.00	(1.60–2.49)	2.69	(2.12–3.43)
Leisure time physical activity (active/inactive)	0.90	(0.73–1.12)	1.06	(0.82–1.37)
Hypertension (yes/no)	1.34	(1.10–1.62)	1.79	(1.44–2.22)

*Alcohol intake (g/day of ethanol): men, ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0; women, ALC_1: 0 < ethanol ≤ 4.9, ALC_2: 4.9 < ethanol ≤ 11.5, ALC_3: ethanol > 11.5. ALC_0: non-drinkers and infrequent occasional drinkers who consume alcohol on three or fewer days a month. 95% CI, 95% confidence interval.

Table 4 Multivariate logistic regression analysis of the 10-year incidence of Type 2 diabetes mellitus in middle-aged Japanese males according to BMI

	BMI ≤ 22 kg/m² (n = 3845)		25 kg/m² ≥ BMI > 22 kg/m² (n = 5671)		BMI ≥ 25 kg/m² (n = 3397)	
	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
Alcohol intake*						
ALC_0	1.00 (referent)		1.00 (referent)		1.00 (referent)	
ALC_1	1.05	(0.55–2.01)	1.12	(0.80–1.56)	1.08	(0.79–1.48)
ALC_2	1.91	(1.05–3.46)	1.16	(0.83–1.61)	1.24	(0.89–1.71)
ALC_3	2.89	(1.63–5.11)	1.17	(0.83–1.66)	1.03	(0.73–1.44)

*Alcohol intake (g/day of ethanol): ALC_1: 0 < ethanol ≤ 23.0, ALC_2: 23.0 < ethanol ≤ 46.0, ALC_3: ethanol > 46.0. 95% CI, 95% confidence interval. Adjusted for age, BMI, cigarette smoking, exercise, family history of diabetes and prevalent hypertension.

50.0 ml/day) to be associated with reduced risk of Type 2 diabetes among men with BMI ≥ 22.1 kg/m², while heavy alcohol consumption was associated with an increased risk among lean men (BMI ≤ 22.0 kg/m²). All the subjects of the Osaka Health Survey were employees of the same company, while the subjects of our study were composed of those living in several areas of Japan. Therefore, the study population in our analysis may be more representative of the general Japanese. However, the heterogeneity of socio-economic status in our cohort could not completely exclude potential confounding on, for example, alcohol consumption.

Recently, three more reports have been published that deal with the relationship between alcohol consumption and the risk of Type 2 diabetes among Japanese [42–44]. One of these reported a significant protective effect of a low level of alcohol consumption (23.0–45.9 g ethanol/day) against development of Type 2 diabetes, i.e. a possible U-shaped association among male employees during 7 years of follow-up [42]. Another study demonstrated a significantly positive association in lean (BMI ≤ 22.0 kg/m²) but no significant association in obese (BMI ≥ 25.0 kg/m²) subjects; and a significant negative association in those who had an intermediate BMI (22.1–24.9 kg/m²) between current alcohol consumption and the incidence of Type 2 diabetes, following male (72%) and female (28%) employees for a mean of 5.7 years [43]. In addition, the Hisayama Study identified alcohol consumption as an independent risk factor for diabetes among males [44]. Summing up the literature and our data, alcohol consumption exceeding 46 g/day is concluded to have an unfavourable effect, prompting Type 2 diabetes development, especially among lean (BMI ≤ 22.0 kg/m²) Japanese men. The apparent lack of an association in women in the present study may be due to the small number of alcohol drinkers among the women surveyed (Table 2).

No significant correlation was found between leisure-time physical activity and diabetes development, a finding somewhat different from other prospectively designed studies, most of which showed a significant association between physical inactivity and Type 2 diabetes [30,37,45–47]. In this context, it may have been a limitation in regard to assessing the association that we categorized subjects only according to frequency of leisure-time exercise in the present study.

Our study has some limitations. First, only self-reported information was available regarding the subject's diabetes status. Although the validation examination showed that self-reported diabetes reflected the true situation fairly well (more than 80%) in this general population, the number of those with undiagnosed diabetes who were in the non-diabetic category according to self-report should be estimated. For this purpose, we compared the number of self-reported diabetic subjects with the number of those who were diagnosed on the basis of plasma glucose and HbA_{1c} levels [23] in a group of approximately 14 000 health check-up examinees involved in the JPHC Cohort I. The results showed that about half of all prevalent cases (self-reported and blood-sample diagnosed combined) were undiagnosed until the health check-up. Thus, the self-report-defined non-diabetic category at follow-up is likely to have contained a substantial undiagnosed population, possibly similar in number to the diabetic category defined by self-report. This implies that the odds ratios observed in our analyses may have underestimated the effect of risk factors on the total incidence of diabetes.

Second, there may be follow-up bias between the diabetic and non-diabetic categories resulting from a presumed excess mortality of the diabetic patients during the follow-up and a possible altered response rate of the patients. We divided the total number of subjects analysed (i.e. those who replied to the baseline questionnaire) into two groups: those who responded to both follow-up questionnaires (74.5% of the initial respondents) and those who did not, and compared the two groups. There were no significant differences in representative parameters, such as BMI and lifestyle characteristics, in either men or women, and therefore estimated incidence of diabetes calculated on the basis of these parameters. This suggests that our results were not seriously affected by follow-up bias.

Third, data for alcohol consumption were obtained from self-reports. Therefore, there might be under-reporting of true alcohol consumption. In this regard, it should be commented that the levels of γ-glutamyltranspeptidase of the subjects of the group where risk for diabetes starts to increase are roughly estimated to have been ranged between ~30 and ~80 IU/l as a whole [19], which correspond to normal to moderately high levels of γ-glutamyltranspeptidase of Japanese male population. Finally, previously diagnosed medical conditions were self-reported by participants, so this study may not exclude subjects with asymptomatic chronic alcoholic liver disease at baseline.

The average annual incidence of Type 2 diabetes by self-report in the current study was calculated as 0.63% among men and 0.34% among women, incidences that, including surmised undiagnosed cases, lie in the lower middle range of the reported crude incidence rate in the Japanese general population (0.2–4.0% per year for both men and women) [48], although age range and diagnostic criteria were different from those of our study. The male predominance of the observed incidence in the present study is another interesting point. Similar results were also obtained in the Japanese Governmental investigations of diabetes conducted in 1997 [49] and in 2002 [50], which were based on 5883 and 5792 subjects from among the participants in the National Nutritional Survey of the year, respectively.

In conclusion, most variables predicting future diabetes in western populations were also found to be important predictors of the disease in our current analyses. However, greater emphasis should be placed on alcohol consumption, as it might have more of an adverse than a beneficial effect on development of diabetes, in comparison with western populations. This may be due to the difference in distribution of polymorphic ethanol-metabolizing enzymes between Japanese and western populations [51,52].

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