厚生労働科学研究研究費補助金
循環器疾患等総合研究事業
（臨床研究実施チームの整備）
厚生労働省多目的コホート班との共同による
糖尿病実態及び発症要因の研究

平成１７年度　総括研究報告書

主任研究者　門脇　孝

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厚生労働科学研究費補助金（臨床研究基盤整備推進研究事業
（若手医師・協力者活用に要する研究）総括研究報告書
厚生労働省多目的コホート班との共同による糖尿病実態及び発症要因の研究

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研究要旨：本研究は、「厚生労働省多目的コホート班との共同による糖尿病実態及び発症要因の研究」（以下、コホート研究）の研究支援およびその応用的臨床研究を行うものである。コホート糖尿病研究は、従来から厚生労働省がん研究助成金「多目的コホートによるがん・循環器疾患の疫学研究」班（班長 津金昌一郎、以下「厚生労働省研究班による多目的コホート研究」と略す）が調査を行っている地域に、糖尿病の実態調査を加えることにより実施するものであり、同班との共同研究として1998年度から行っている。
(1)糖尿病調査とその解析：1998-2000および2003-2005年度に、質問紙及びHbA1cの測定により約24000名の対象者に対して糖尿病有病率を把握する。糖尿病の把握は老人保健法検診に含まれている血糖値（随時(空腹時を含む)）に加え、この質問紙法およびHbA1cの測定により把握する。ベースライン調査（1998-2000年度）、5年後調査（2003-2005年度）の2回の調査により、糖尿病発症率を把握する。さらに、これらを用い、前向きコホート研究、断面研究のデザインにより生活習慣等との関係を分析する。
(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析：「厚生労働省研究班による多目的コホート研究」データとの包括的解析を行い、糖尿病発症と生活習慣等との関係を明らかにする。
(3)採択された課題に関連する臨床研究：
さらに、申請する研究実施チームの整備により、これまでの研究成果などから得られた知見を実証する臨床研究を行う。

A. 研究目的

糖尿病の罹患者数は約740万人とわが国の高齢者における主要な疾患であり、糖尿病は心筋梗塞・脳卒中のリスク増大を介して日本人の健康寿命を短縮する最大の原因のひとつとなっている。今後の本格的な高齢化社会の到来を前にして、医療費の増大を抑制し国民の活力を維持するためには、糖尿病の実態を明らかにし、どの様な生活習慣などの環境因子が糖尿病を発症・進展させているかについて探索的な研究を行なうことの必要性がますます高まっている。

本研究は、厚生労働省研究班による多目的コホート研究によって得られたデータから糖尿病発症・進展において重要な役割を担っている生活習慣を網羅的・体系的に解析するとともに、重要と考えられる生活習慣については個別に臨床試験を立ち上げその意義を明らかにすることを目的とする。本研究では、次のような成果が得られることが期待される。

(1) 糖尿病・メタボリックシンドロームを発症・進展させる生活習慣が明らかになる。更に、どのような生活習慣によってどの程度糖尿病・メタボリックシンドロームの発症リスクが上昇するかが明らかになる。本研究の成果を利用して将来的には、簡単な問診によって糖尿病・メタボリックシンドローム発症のハイリスク者をスクリーニングできるようなスコアリング法が開発される。

(2)糖尿病やメタボリックシンドロームの病態を簡便かつ早期・正確に診断する測定キットの臨床的妥当性が明らかになり、糖尿病・メタボリックシンドロームの診断において広く普及することが期待される。(1)(2)の成果は、糖尿病やメタボリックシンドローム診療のガイ

ドラインや国の生活習慣病対策法を策定する際にも重要な基盤的データとなることが期待される。日本における糖尿病罹患者数の多さと糖尿病に伴う合併症によるQOL（生活の質）低下、心筋梗塞・脳卒中による寿命の短縮を合わせて考えると、本研究による成果は社会的な波及効果が極めて高いと考えられる。

B. 研究方法

(1) 糖尿病調査とその解析（a組）ならびに（b組）：

◆スキーム1（9コホート）：1998-2000年度に、質問紙及びHbA1cの測定により糖尿病有病率を把握する。5年後（平成2003-05年度）にも同様の調査を行い糖尿病発症率を把握する。これらを用いて前向きコホート研究、断面研究のデザインにより生活習慣等との関係を分析する。

◆スキーム2：スキーム1対象地域を含む全コホートにおいて糖尿病実態調査を行う。スキーム1の対象以外の地域では、2000年度にスキーム1対象地域と同様の調査（質問紙、血糖値、HbA1cの測定）を行う。対象者総数に対し、HbA1cおよびこれで定義された糖尿病を曝露要因として、虚血性心疾患、脳卒中、癌等への危険因子としての役割を、「厚生労働省多目的コホート研究」班の疾患登録システムから得られた罹患データを用いて前向きコホート研究にて検討する。

(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析：

「厚生労働省研究班による多目的コホート研究」データとの包括的解析を行い、生活習慣等との関係を明らかにする。以上の（1）及び（2）について、今回申請する臨床研究実施チーム（a組）～（c組）がその実施面を担当する。すなわち、これらのチームが上記の調査・解析を実際に施行し、またはこれをサポートする。

(3) 採択された課題に関連する臨床研究：申請する研究実施チームの整備により、これまでの研究成果などから得られた知見を実証すると共にその簡便な診断法としてのバイオマーカーの臨床的意義を検討する臨床研究を予定する。具体的には、①検査データ、嗜好と体格に関する研究（a組：野田）：主研究で得られた検診などの検査データと、嗜好や体格との関係を検討する。対象：600人。②運動と血糖コントロールに関する研究（b組：高橋）：主研究から得られた運動の重要性を教育入院の期間で検討する。20例を対象予定とする。③糖尿病・メタボリックシンドロームの発症・進展を予測するバイオマーカーの開発（c組：原）：血中アディポカインの糖尿病・メタボリックシンドロームを診断する感度・特異度など臨床応用のための基礎的データについては収集できた。今年度はグルコースクランプ法によるインスリン抵抗性・MRIによる骨格筋・肝臓の中性脂肪含量との相関を検討し、より臨床的に有用なバイオマーカーの開発を行なう。

C. 研究結果

(1) 糖尿病調査とその解析

◆スキーム1：平成10～12年度に行なった「厚生労働省研究班による多目的コホート」対象の健診受診者による糖尿病

調査(ベースライン調査；対象者約2万5千人)の結果、糖尿病有病率を51～70歳では男性13～15%、女性6～9%と確定した。
平成15～17年度に第2回目の糖尿病実態調査(5年後調査)を全国10箇所で実施、終了し現在データを収集・解析中である。

(2)「厚生労働省研究班による多目的コホート研究」データとの包括的解析および臨床研究

① 好と体格に関する研究（a組：野田)：平成2年、7年、12年に行なわれた「厚生労働省研究班による多目的コホート(コホートⅠ)」のベースライン調査、5年後調査、10年後調査のアンケートの結果を用い、自己申告による10年間の糖尿病発症に対する危険因子を前向きコホート研究のスタディデザインによって分析した。その結果、年齢、BMI、糖尿病の家族歴は多重ロジステイック解析に予知男女とも糖尿病の発症と有意に正相関した。喫煙（過去の喫煙と現在20本以上の喫煙）も男女いずれにおいても糖尿病発症のリスクを有意に上げていた。男性では、1日のエタノール摂取が23g(日本酒換算1合)以上のものにおいて、糖尿病発症のリスクが有意に上昇していた。とくに、痩せ型（BMI22以下）の男性において1合/日以上の飲酒が2型糖尿病と正相関した。喫煙に関しては、BMI２２以上、特に25以上の男性において2型糖尿病の発症と相関が強く、障害喫煙量と糖尿病発症リスクとの間には容量・反応関係が認められた。さらに、そのリスクは禁煙により10年で非喫煙者とほぼ同等になることを見出した。
さらに、コーヒー摂取はコーヒー非摂取者に比し、その後の糖尿病発症が男女ともに有意に低かった（男性 0.83 (95%CI 0.70-0.99)、女性 0.76 (95%CI 0.61-0.94)。ベースライン調査のアンケートと健診データを用いた横断研究においては、コーヒー摂取(杯数、カフェイン換算)、総カフェイン摂取量は空腹時高血糖と有意な負の相関を示した(緑茶、紅茶、ウーロン茶は相関を示さなかった)。男女別に、コーヒーにや紅茶に砂糖を入れる習慣の有無と喫煙習慣を加えた解析を行ない、砂糖についての習慣、現在の喫煙習慣の要因を加えても、男性においてコーヒー摂取が空腹時高血糖と有意に相関した(砂糖に関する習慣、喫煙はいずれも有意な結果を示さなかった)。

② 運動と血糖コントロールに関する研究（b組：高橋)：「厚生労働省研究班による多目的コホート研究」における運動について調査項目の妥当性の検討を行なっている。調査は、1）過去に行なったものと同一の質問表による調査を2度にわたって実施することにより、質問表の再現性について検討する。この際、「24時間行動記録表」および「運動加速度計(ライフコーダ)」よる評価も同時に行い、それらの変動についても検討する、2)質問票から計算したエネルギー消費量を「24時間行動記録表」および「運動加速度計(ライフコーダ)」で算出したエネルギー消費量と比較し、妥当性を検

討する、というものである。その結果、「24 時間行動記録」による energy expenditure (EE: METs/day)の再現性はよいこと(Spearman's correlation coefficient = 0.91 ($p<0.0001$)や、質問票による EE と「24 時間行動記録」によるそれとの間には有意な相関(ρ =0.48～0.62)が認められること、「運動加速度計(ライフコーダ)」による EE と「24 時間行動記録」によるそれとの間の相関は低い(ρ =0.13)こと、などの知見を得ている。

③ 糖尿病・メタボリックシンドロームの発症・進展を予測するバイオマーカーの開発 (c 組：原)：これまでインスリン抵抗性を増悪させると報告されているアディポカインについては、インスリン抵抗性と有意に相関するものは認めなかった。

D. 考察

家族歴、喫煙は男女いずれにおいても糖尿病発症のリスクを上昇させる。痩せ型 (BMI22 以下) の男性においては 1 合/日以上の飲酒が 2 型糖尿病と正相関した。また、喫煙に関しては、肥満男性において 2 型糖尿病の発症と相関が強く、生涯喫煙量と糖尿病発症リスクとの間には容量・反応関係が認められた。さらに、そのリスクは禁煙により 10 年で非喫煙者とほぼ同等になる。さらに、コーヒー摂取はコーヒー非摂取者に比し、その後の糖尿病発症が男女ともに有意に低かった。

E. 結論

男女とも糖尿病の家族歴、喫煙が、痩せ型の男性においては、飲酒は糖尿病の発症リスクを上昇させる。コーヒー摂取は逆に糖尿病の発症リスクを低下させる。

F. 健康危険情報

特になし

G. 研究発表

1. 論文発表

1) Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A, Ohashi Y, Kadowaki T, S. Tsugane, for the JPHC Study Group: Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in JPHC Study Cohort I. ***Diabetic Medicine*** 22: 323-331, 2005.

2. 学会発表

なし

H. 知的財産権の出願・登録状況

(ア) 特許出願

なし

(イ) 実用新案登録

なし

(ウ) その他

なし

III. 研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A, Ohashi Y, Kadowaki T, S. Tsugane, for the JPHC Study Group	***Diabetic Medicine***	Diabetes Care	**22**	323-331	2005

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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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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

Characteristics	Men			Women		
	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/m^2-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/m^2 (n = 3845)		25 kg/m^2 ≥ BMI > 22 kg/m^2 (n = 5671)		BMI ≥ 25 kg/m^2 (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/m^2, while heavy alcohol consumption was associated with an increased risk among lean men (BMI ≤ 22.0 kg/m^2). 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/m^2) but no significant association in obese (BMI ≥ 25.0 kg/m^2) subjects; and a significant negative association in those who had an intermediate BMI (22.1–24.9 kg/m^2) 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/m^2) 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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