morning urine. Taken together with these studies, the data suggest that the current treatment by diabetologists along with administration of the usual hypoglycaemic and hypotensive drugs from the stage of normoalbuminuria or low microalbuminuria reduced the annual incidence of proteinuria to a level as low as 0.67/100 person-years. Ideally, however, the inclusion of a control group receiving placebo and matched to the drug-treated diabetic patients would be desirable in order to allow a firm conclusion to be drawn, although admittedly this would be ethically problematic. As the baseline UACR profoundly affected the cumulative incidence of proteinuria, it might be clinically useful to divide patients with microalbuminuria into low- and high-risk groups, i.e. those with low and high microalbuminuria, although the cut-off value remains to be determined.

In the present study, progression to proteinuria was independently associated with higher baseline $HbA_{1c}$ and SBP levels in addition to an elevated baseline UACR. Furthermore, smoking was also a significant predictor of proteinuria. These results are consistent with previous studies [11, 15]. In the UKPDS, the risk factors most highly associated with proteinuria were reported to be urinary albumin, plasma creatinine, waist circumference, SBP, glycaemic control, LDL-cholesterol, and plasma triacylglycerol [15]. Indian-Asian ethnicity was also an independent risk factor for microalbuminuria and/or proteinuria [12, 15]. Smoking and male sex were reported to be independent predictors of proteinuria in addition to plasma cholesterol, mean blood pressure and $HbA_{1c}$ [11]. Based on these epidemiological studies, tight glycaemic control has been reported to be effective for preventing the onset and/or progression of nephropathy in clinical trials such as the Diabetes Control and Complications Trial (DCCT), the Kumamoto study and the UKPDS [16–18]. Strict blood pressure control, especially with ACE inhibitors or ARBs, has also been demonstrated to be effective for delaying the progression of diabetic nephropathy [6, 7, 19–21]. However, in the present study, the initial usage of an ACE inhibitor and/or ARB, or statin was not significantly associated with the prevention of proteinuria. As this study was designed to clarify the effects of lifestyle intervention on subsequent occurrence of diabetic complications, it might have been difficult to recognise the effects of such drugs on the progression of diabetic nephropathy. In some studies, normalisation of microalbuminuria, i.e. remission/regression, has also been reported [6, 12]. In fact, in our study, 30.3% of 452 individuals with low microalbuminuria demonstrated normalisation.

However, following the advent of modern therapeutics, especially hypoglycaemic and antihypertensive agents, diabetic nephropathy is the most common cause of ESRD, and the number of patients being started on haemodialysis is still increasing dramatically in many countries, particularly in Asia. Our data have major clinical relevance because we have demonstrated that the initiation of hypoglycaemic and antihypertensive treatment from the early stage of nephropathy might lower the rate of transition to proteinuria even in the Japanese, who are highly susceptible to diabetic nephropathy. To reduce the number of patients who require haemodialysis, it is very important to measure UACR, make a diagnosis of diabetic nephropathy, define the stage of nephropathy and initiate strict glycaemic and blood pressure control as early as at the normo- or low-microalbuminuria stage.

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**Duality of interest** The authors declare that there is no conflict of interest associated with the manuscript.



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# Serum Level of Triglycerides Is a Potent Risk Factor Comparable to LDL Cholesterol for Coronary Heart Disease in Japanese Patients with Type 2 Diabetes: Subanalysis of the Japan Diabetes Complications Study (JDCS)

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**Context:** Risk factors for cardiovascular complications in Japanese patients with diabetes have not been fully elucidated.

**Objective:** Our objective was to determine incidence of and risk factors for coronary heart disease (CHD) and stroke in Japanese diabetic patients.

**Design and Settings:** We conducted a prospective study at 59 hospitals throughout Japan.

**Patients:** Patients included 940 men and 831 women with type 2 diabetes (mean age, 58.2 yr) without a history of cardiovascular complications who were followed for a median of 7.86 yr.

**Intervention:** This was an observational study.

**Main Outcome Measures:** Incidence of CHD and stroke was evaluated.

**Results:** Incidences of CHD and stroke per 1000 person-years were 9.59 and 7.45, respectively, whereas those of myocardial and brain infarctions were 3.84 and 6.29, respectively. Multivariate Cox analysis revealed that the serum log-transformed triglyceride level was a potent and independent predictor of CHD [hazard ratio (HR) = 1.54; 95% confidence interval (CI) = 1.22–1.94 per 1 SD increase), comparable to low-density lipoprotein (LDL) cholesterol (HR = 1.49; 95% CI = 1.25–1.78 per 1 SD increase). Triglycerides and LDL cholesterol linearly and continuously increased CHD risk, and subjects in the top third for both had markedly high risks of CHD, and their effects were possibly additive. However, serum triglycerides worked independently of blood pressure levels. Systolic blood pressure was the only significant predictor for stroke except for age (HR = 1.31; 95% CI = 1.04–1.65, per 1 SD increase).

**Conclusions:** In Japanese patients with type 2 diabetes, the serum triglyceride level was a leading predictor of CHD, comparable to LDL cholesterol. Because the serum triglyceride level is not a leading predictor of CHD in diabetic subjects in Western countries, ethnic group-specific strategies for prevention of diabetic macroangiopathy may be indicated. (*J Clin Endocrinol Metab* 96: 0000–0000, 2011)

As in other regions of the world, type 2 diabetes also confers a substantially enhanced risk of cardiovascular disease (CVD) in East Asia where the diabetic population has been explosively increasing (1). Compared with type 2 diabetic patients in Western countries, those in East Asian countries, including Japan, are suggested to have different features regarding cardiovascular complications. Diabetic patients in East Asia have a much lower incidence of coronary heart disease (CHD) than those in Western countries (2), and CVD is not necessarily a lead-

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Abbreviations: CHD, Coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UKPDS, United Kingdom Prospective Diabetes Study.

ing cause of mortality among diabetic patients in Japan (3). However, the incidence of stroke in East Asia, which includes Japan, is higher than that of myocardial infarction, which is opposite to what has been observed among Western diabetic subjects (2). In addition, as we previously reported, many other traits regarding cardiovascular complications differ considerably between Western and Japanese diabetic populations, such as the influence of metabolic syndrome (4, 5) or alcohol drinking (6), the relationship between predictors for macro- and microvascular complications (7), or the degree of obesity (8, 9), which is closely associated with insulin resistance and atherosclerosis.

Risk factors for cardiovascular complications in diabetic subjects have been predominantly reported in White, Black, and Hispanic subjects in Western countries, but those issues in East Asians, including Japanese, with diabetes have not been fully elucidated. In particular, although the serum triglyceride level seems to have a significant influence on cardiovascular complications in diabetic subjects in East Asia (10–12), it has not been confirmed by large-scale prospective studies. Clarifying those issues could contribute to ethnic group-specific diabetes care and prevention of cardiovascular disease for those of Asian origin, who account for more than 60% of the world's diabetes population (1). Therefore, we investigated the association between risk factors and the incidence of CHD and stroke in a nationwide clinical trial of Japanese patients with type 2 diabetes mellitus.

## Patients and Methods

### Recruitment of patients

The present analysis was conducted as part of the Japan Diabetes Complications Study, a multicenter prospective study on the incidence of and risk factors for macro- and microvascular complications among Japanese patients with type 2 diabetes (4). For this analysis of macrovascular complications, 940 men (mean age 57.8 ± 7.1 yr) and 831 women (mean age 58.7 ± 6.8 yr) who registered from January 1995 to March 1996 from outpatient clinics in 59 university and general hospitals nationwide that specialize in diabetes care were selected after consideration of the exclusion criteria prespecified in the study protocol. Excluded were patients with impaired glucose tolerance, a history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia, type III hyperlipidemia (diagnosed by broad β-band on electrophoresis) or nephrotic syndrome (urine protein ≥3.5 g/d and serum total protein ≤6.0 mg/dl), and serum creatinine levels greater than 1.3 mg/dl (120 μmol/liter).

Diabetes mellitus and impaired glucose tolerance were diagnosed according to the Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus, which is almost identical in terms of cutoff values for glucose levels to those of the World Health Organization (WHO). The protocol for the study, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health Labor and Welfare, received ethical approval from the institutional review boards of all of the participating institutes. Written informed consent was obtained from all patients enrolled.

### Clinical and laboratory measurements

Patients were assessed yearly after the baseline evaluation. Mean values of at least two measurements each year were obtained for glycated hemoglobin (HbA1c), fasting plasma glucose, and fasting serum lipids. HbA1c assays were performed according to procedures outlined by the Laboratory Test Committee of the Japan Diabetes Society with the standard samples supplied by the society, which is known to be converted by the formula HbA1c (Japan Diabetes Society) (percent) = HbA1c (National Glycohemoglobin Standardization Program) (percent) − 0.4%, with 5.8% as the upper limit of normal. All other laboratory tests were done at each participating institute. Serum low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's equation, except where triglycerides exceeded 400 mg/dl, in which case the LDL cholesterol data were treated as missing. This was applicable to 20 subjects. The estimated glomerular filtration rate (GFR) was calculated according to the following equation generated by The Japanese Society of Nephrology: GFR (milliliter per minute per 1.73 $m^2$) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) (13). All other measurements, including those for body weight, blood pressure, and waist/hip circumference, were done at least once yearly. Waist and hip circumferences were measured at the levels of the umbilicus and trochanters, respectively. A 12-lead electrocardiogram (ECG) and chest x-ray were performed annually. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a self-administered questionnaire.

### Outcome measures

The outcomes considered in the analysis were a fatal or first nonfatal manifestation of CHD or stroke, all of which were diagnosed yearly by predefined criteria (4). CHD consists of angina pectoris and myocardial infarction, and their diagnoses were according to criteria defined by the WHO/MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project (14, 15), and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by use of nitroglycerine as validated by an exercise-positive

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ECG and/or angiography. A patient with a first percutaneous coronary intervention or coronary artery bypass graft was also counted as having a CHD event.

Diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labor, and Welfare of Japan (16) and WHO criteria (17). Stroke events were defined as a constellation of focal or global neurological deficits or disturbance of cerebral function that was sudden or rapid in onset and for which there was no apparent cause other than a vascular accident such as epilepsy or brain tumors on the basis of a detailed history, neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (17). No cases of asymptomatic lesions detected by brain imaging (*i.e.* silent infarction) were included. Only first-ever CHD or stroke events during the study period were counted in the analysis and in a patient having both CHD and stroke events; each event was counted separately. Information regarding primary outcome and other clinical parameters for each subject was collected through an annual report from each physician. Adjudication of endpoints was made by central committees comprised of experts in each complication who were masked as to risk factor status based on additional data such as computed tomography or magnetic resonance imaging of the brain or sequential changes in ECG.

### Statistical analysis

All statistical analyses and data management were conducted at a central data center. Patient characteristics were described as mean ± SD, median, interquartile range, or percentage. After dividing subjects into three groups, *i.e.* CHD, stroke, or no CVD (subject with neither CHD nor stroke), we compared the no-CVD group with the CHD or stroke groups separately by Dunnett's *t* test and Fisher's exact test for numerical and categorical variables, respectively. Univariate and multivariate Cox regression analyses were used to estimate the adjusted hazard ratios (HR) and 95% confidence intervals (CI) for risk factors. A histogram was used to check normality of distributions of these variables. The distributions of triglycerides and lipoprotein(a) were skewed, and we conducted Cox analysis using the log-transformed values after confirming their normality instead of using the raw data. To directly compare the impact of risk factors that have different units or means, we also calculated the HR per 1 SD increment for most variables. To explore potential nonlinear relationships, we used multivariate-adjusted generalized additive models with a spline function of three degrees of freedom. All *P* values are two sided, and the significance level is 0.05. All statistical analyses were conducted using SAS packages version 9.2 (SAS Institute Inc., Cary, NC).

## Results

Table 1 summarizes the baseline characteristics according to the occurrence of CHD and stroke events. During the median follow-up period of 7.86 yr, the total person-years studied were 11,743 (6106 for men and 5637 for women), and the crude incidence per 1000 patient-years of all CHD was 9.59 (11.18 in men and 7.85 in women), and among those with CHD, that of myocardial infarction was 3.84 (4.95 in men and 2.62 in women). The crude incidence per 1000 patient-years of all strokes was 7.45 (8.70 in men and 6.07 in women); among these, the incidence of brain infarction was 6.29 (7.44 in men and 5.03 in women). In terms of therapeutic measures, the proportion of patients who were being administered antihypertensive agents was significantly higher among those in whom CHD or stroke occurred, and the proportion of patients receiving biguanides was more than double in patients with stroke in comparison with those who did not experience these events.

HR with a 95% CI of each factor for CHD and stroke events estimated by the Cox regression analysis are shown in Table 2. In multivariate analysis for CHD, serum levels of both LDL cholesterol and log-transformed triglycerides were the most significant and the strongest predictors, having almost identical HR of 1.5 with an increment of 1 SD of each variable. These results were fundamentally the same even when the HR were calculated with an increment of 1 mmol/liter of these lipid variables [LDL cholesterol, 1.64 (95% CI = 0.33–2.02), $P < 0.001$; triglycerides, 1.63 (95% CI = 1.29–2.07), $P < 0.001$]. HbA1c and systolic blood pressure had borderline significance, with *P* values <0.1. With regard to stroke, except for age, systolic blood pressure was the only other significant predictor. Spline curves of the HR with 95% CI between CHD events and LDL cholesterol or triglyceride levels (Fig. 1) demonstrated linear positive relationships for both lipid variables.

Because the serum triglyceride level was found to be a characteristically strong predictor for CHD in our cohort, we investigated the combined roles of triglycerides with other major risk factors for CHD (Fig. 2). In comparison with subjects in the bottom third of both triglyceride values and either body mass index, HbA1c, systolic blood pressure, or LDL cholesterol as the reference (reference HR = 1), the risk for CHD in subjects with values in the top third for both triglycerides and either of these factors was approximately three times higher, which is statistically significant. Subjects in the top third for triglycerides were at a significantly high risk of CHD regardless of the concurrent systolic blood pressure levels. In contrast, subjects in the top third for both triglycerides and LDL cholesterol had a markedly high risk of CHD, and their effects were possibly additive, although the *P* value for interaction was 0.66. HbA1c also appears to work additively with triglycerides for CHD risk, but their interaction was not statistically significant.

**TABLE 1.** Patient characteristics at baseline according to occurrence of CHD and stroke events (mean ± SD)

| | No CVD | CHD | *P* value (*vs.* no CVD) | Stroke | *P* value (*vs.* no CVD) |
|---|---|---|---|---|---|
| No. of patients (no. of women) | 1577 (757) | 109 (41) | 0.036[a] | 85 (33) | 0.099[a] |
| Age (yr) | 58.2 ± 7.0 | 59.8 ± 6.5 | 0.037 | 60.7 ± 6.1 | 0.003 |
| Diabetes duration (yr) | 10.8 ± 7.2 | 11.7 ± 6.8 | 0.38 | 11.0 ± 6.9 | 0.97 |
| BMI (kg/m$^2$) | 23.0 ± 3.0 | 23.4 ± 2.8 | 0.35 | 23.6 ± 3.1 | 0.087 |
| Waist circumference (cm) | 79.1 ± 9.2 | 81.6 ± 8.2 | 0.017 | 81.9 ± 8.7 | 0.017 |
| Systolic blood pressure (mm Hg) | 131 ± 16 | 135 ± 16 | 0.028 | 138 ± 16 | <0.0001 |
| Diastolic blood pressure (mm Hg) | 76 ± 10 | 79 ± 9 | 0.068 | 79 ± 9 | 0.079 |
| Fasting plasma glucose (mmol/liter)) | 8.8 ± 2.4 | 9.2 ± 2.5 | 0.20 | 9.2 ± 2.7 | 0.39 |
| HbA1c (%) | 7.9 ± 1.3 | 8.1 ± 1.4 | 0.077 | 8.1 ± 1.4 | 0.17 |
| Serum LDL cholesterol (mmol/liter) | 3.1 ± 0.8 | 3.5 ± 0.8 | <0.0001 | 3.2 ± 1.0 | 0.84 |
| Serum HDL cholesterol (mmol/liter) | 1.4 ± 0.5 | 1.3 ± 0.4 | 0.031 | 1.4 ± 0.4 | 0.30 |
| Serum triglycerides (mmol/liter)[b] | 1.1 (0.8) | 1.4 (0.8) | 0.016 | 1.3 (0.7) | 0.25 |
| Serum lipoprotein(a) (μmol/liter)[b] | 0.81 (1.1) | 0.95 (1.1) | 0.56 | 1.0 (1.0) | 0.049 |
| Estimated GFR (10 ml/min · 1.73 m$^2$) | 87.4 ± 28.9 | 82.0 ± 29.5 | 0.12 | 91.2 ± 33.8 | 0.42 |
| Therapeutic measures | | | | | |
| Diabetes | | | | | |
| Diet only (%) | 18.6 | 14.7 | 0.31 | 14.1 | 0.30 |
| Insulin (%) | 21.7 | 25.7 | 0.33 | 23.5 | 0.68 |
| Sulfonylureas (%) | 57.2 | 62.4 | 0.29 | 58.8 | 0.76 |
| α-Glucosidase inhibitors (%) | 20.3 | 22.0 | 0.67 | 21.2 | 0.85 |
| Biguanides (%) | 5.1 | 1.6 | 0.21 | 13.5 | 0.026 |
| Insulin sensitizer (%) | 2.0 | 3.7 | 0.26 | 1.2 | 0.59 |
| Antihypertensive agents (%) | 24.7 | 34.9 | 0.018 | 35.7 | 0.023 |
| Agents for dyslipidemia (%) | 23.8 | 29.4 | 0.19 | 25.0 | 0.79 |
| Diet | | | | | |
| Energy intake (kJ/d)[b] | 7079 (2248) | 6801 (1903) | 0.67 | 7259 (2726) | 0.97 |
| Fat intake (g/d)[b] | 51 (21) | 52 (18) | 0.59 | 53.6 (28) | 0.50 |
| Exercise (kJ/d)[b] | 530 (1112) | 577 (1020) | 0.91 | 442 (922) | 0.73 |
| Current smoker (%) | 26.7 | 37.1 | 0.021 | 32.1 | 0.29 |
| Alcohol intake: never, ≤3 drinks, >3 drinks (%)[c] | 62.8/31.0/6.2 | 61.1/34.3/4.6 | 0.66 | 53.6/35.7/10.7 | 0.13 |

[a] *P* values for differences in gender proportion.

[b] Median (interquartile range).

[c] One drink is equivalent to 12.6 g ethanol based on the U.S. Department of Agriculture definition.

## Discussion

The current analysis of data from the nationwide study of Japanese subjects with type 2 diabetes demonstrated an approximately 1.6-fold increased CHD risk for an increment of 1 mmol/liter in LDL cholesterol, which is almost identical to what is observed in the United Kingdom Prospective Diabetes Study (UKPDS) (18). However, a striking difference between results of this study and those of the UKPDS (18) was that in our cohort, the serum triglyceride level was an additional strong predictor for CHD, showing almost the same 1.5-fold increased risk for the same 1 SD increment as with LDL cholesterol. In the current study, the inclines of the spline curves for LDL cholesterol and triglyceride levels are quite similar, indicating that both lipid variables equivalently affected CHD events in our cohort. The curve for triglycerides demonstrated that when a triglyceride level of 1.1 mmol/liter (100 mg/dl) is defined as a reference, its concentration as low as approximately 1.5 mmol/liter (134 mg/dl) could represent a significant CHD risk, which is quite close to the therapeutic target suggested in the current guidelines, which is 1.68 mmol/liter (150 mg/dl).

Although it is true that the serum triglyceride level is an established independent cardiovascular risk factor in general populations in Western (19) as well as in Asian (20) countries, it is well recognized that its potency as a CHD predictor is not as strong as that of LDL cholesterol (21). Actually, serum triglycerides were not among the significant CHD predictors in the UKPDS patients (18). On the other hand, among East Asians with diabetes, serum triglyceride values have been suggested to have stronger associations with cardiovascular morbidity (10, 12) and mortality (11) than those of LDL cholesterol, although these studies were either cross-sectional (10, 12) or relatively small scale and short term (11). Those results (10–12), together with results of the current relatively large-scale, long-term prospective study, strongly indicate that the serum triglyceride level is one of the leading predictors of CHD and is comparable to LDL cholesterol in East Asian subjects with type 2 diabetes. In this sense, although

**TABLE 2.** HR with 95% CI of each factor for CHD and stroke risk analyzed by Cox models

| | Adjusted by age and sex | | | | | | Multivariate adjusted[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CHD | | | Stroke | | | CHD | | | Stroke | | |
| | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Gender (female; reference is men) | 0.68 | 0.47–1.00 | 0.05 | 0.61 | 0.39–0.94 | 0.03 | 0.57 | 0.35–0.92 | 0.02 | 0.67 | 0.38–1.18 | 0.17 |
| Age (per 5 yr) | 1.16 | 1.01–1.34 | 0.04 | 1.24 | 1.05–1.46 | 0.01 | 1.16 | 1.00–1.35 | 0.06 | 1.30 | 1.09–1.57 | <0.01 |
| Diabetes duration (per 10 yr) | 1.10 | 0.86–1.42 | 0.45 | 0.84 | 0.62–1.15 | 0.27 | 1.26 | 0.96–1.64 | 0.09 | 0.88 | 0.63–1.23 | 0.44 |
| Energy intake (per 418 kJ/d) | 1.01 | 0.96–1.07 | 0.65 | 0.99 | 0.93–1.06 | 0.75 | 1.01 | 0.96–1.07 | 0.68 | 0.98 | 0.92–1.05 | 0.58 |
| Exercise (per 418 kJ/d) | 0.96 | 0.89–1.04 | 0.36 | 0.99 | 0.92–1.08 | 0.87 | 0.98 | 0.91–1.06 | 0.58 | 1.01 | 0.93–1.10 | 0.78 |
| Current smoker (yes; reference is no) | 1.39 | 0.90–2.15 | 0.14 | 1.21 | 0.74–1.98 | 0.46 | 1.41 | 0.91–2.17 | 0.12 | 1.18 | 0.70–1.97 | 0.53 |
| Alcohol drinking status[b] | | | | | | | | | | | | |
| ≤3 drinks (reference) | 1.00 | | | 1.00 | | | 1.00 | | | 1.00 | | |
| >3 drinks | 0.78 | 0.33–1.85 | 0.57 | 1.59 | 0.78–3.26 | 0.20 | 0.59 | 0.24–1.44 | 0.24 | 1.50 | 0.66–3.39 | 0.34 |
| Nondrinker | 1.13 | 0.73–1.75 | 0.60 | 0.87 | 0.52–1.45 | 0.59 | 0.91 | 0.58–1.42 | 0.66 | 1.12 | 0.65–1.91 | 0.68 |
| Body mass index | | | | | | | | | | | | |
| Per 1 kg/m$^2$ | 1.04 | 0.98–1.11 | 0.22 | 1.06 | 0.98–1.13 | 0.13 | 1.00 | 0.93–1.08 | 1.00 | 1.00 | 0.92–1.08 | 0.95 |
| Per 1 SD | 1.13 | 0.93–1.36 | | 1.18 | 0.95–1.46 | | 1.00 | 0.80–1.25 | | 0.99 | 0.78–1.27 | |
| Waist circumference | | | | | | | | | | | | |
| Per 10 cm | 1.24 | 0.99–1.55 | 0.06 | 1.31 | 1.02–1.67 | 0.04 | 1.18 | 0.81–1.73 | 0.39 | 1.21 | 0.79–1.84 | 0.39 |
| Per 1 SD | 1.22 | 0.99–1.49 | | 1.28 | 1.02–1.60 | | 1.17 | 0.82–1.65 | | 1.19 | 0.81–1.75 | |
| Systolic blood pressure | | | | | | | | | | | | |
| Per 10 mm Hg | 1.12 | 1.00–1.26 | 0.05 | 1.20 | 1.06–1.37 | 0.01 | 1.11 | 0.98–1.26 | 0.09 | 1.18 | 1.03–1.36 | 0.02 |
| Per 1 SD | 1.21 | 1.00–1.45 | | 1.36 | 1.09–1.68 | | 1.19 | 0.97–1.45 | | 1.31 | 1.04–1.65 | |
| Diastolic blood pressure | | | | | | | | | | | | |
| Per 10 mm Hg | 1.17 | 0.97–1.40 | 0.10 | 1.20 | 0.97–1.48 | 0.10 | 1.02 | 0.80–1.30 | 0.87 | 0.93 | 0.71–1.21 | 0.57 |
| Per 1 SD | 1.17 | 0.97–1.40 | | 1.19 | 0.97–1.47 | | 1.02 | 0.80–1.30 | | 0.93 | 0.71–1.21 | |
| Estimated GFR | | | | | | | | | | | | |
| Per 10 ml/min · 1.73 m$^2$ | 0.95 | 0.88–1.02 | 0.15 | 1.06 | 1.00–1.13 | 0.07 | 0.95 | 0.89–1.03 | 0.19 | 1.05 | 0.99–1.13 | 0.12 |
| Per 1 SD | 0.85 | 0.69–1.06 | | 1.19 | 0.99–1.43 | | 0.87 | 0.70–1.08 | | 1.17 | 0.96–1.41 | |
| HbA1c | | | | | | | | | | | | |
| Per 1% | 1.21 | 1.06–1.38 | 0.00 | 1.17 | 1.01–1.35 | 0.03 | 1.15 | 1.00–1.33 | 0.05 | 1.11 | 0.94–1.31 | 0.24 |
| Per 1 SD | 1.28 | 1.08–1.51 | | 1.23 | 1.02–1.48 | | 1.20 | 1.00–1.45 | | 1.14 | 0.92–1.42 | |
| Fasting plasma glucose | | | | | | | | | | | | |
| Per 1 mmol/liter | 1.08 | 1.01–1.16 | 0.04 | 1.07 | 0.99–1.17 | 0.11 | 0.99 | 0.91–1.09 | 0.90 | 1.02 | 0.91–1.13 | 0.75 |
| Per 1 SD | 1.21 | 1.01–1.44 | | 1.19 | 0.96–1.46 | | 0.99 | 0.79–1.23 | | 1.04 | 0.80–1.35 | |
| LDL cholesterol | | | | | | | | | | | | |
| Per 1 mmol/liter | 1.71 | 1.39–2.10 | <0.01 | 1.05 | 0.80–1.37 | 0.74 | 1.61 | 1.30–1.98 | <0.01 | 1.00 | 0.76–1.32 | 1.00 |
| Per 1 SD | 1.56 | 1.32–1.86 | | 1.04 | 0.83–1.30 | | 1.49 | 1.25–1.77 | | 1.00 | 0.79–1.26 | |
| HDL cholesterol | | | | | | | | | | | | |
| Per 1 mmol/liter | 0.57 | 0.35–0.93 | 0.02 | 0.68 | 0.40–1.16 | 0.15 | 0.99 | 0.56–1.74 | 0.97 | 0.86 | 0.46–1.61 | 0.64 |
| Per 1 SD | 0.78 | 0.63–0.97 | | 0.85 | 0.67–1.07 | | 1.00 | 0.78–1.27 | | 0.94 | 0.72–1.23 | |
| Log–triglycerides (per 1 SD) | 1.39 | 1.16–1.65 | <0.01 | 1.20 | 0.97–1.47 | 0.09 | 1.54 | 1.22–1.94 | <0.01 | 1.13 | 0.86–1.46 | 0.38 |
| Log–Lp(a) (per 1 SD) | 1.22 | 0.99–1.49 | 0.06 | 1.14 | 0.91–1.44 | 0.25 | 1.15 | 0.93–1.43 | 0.20 | 1.17 | 0.92–1.49 | 0.19 |

[a] Adjusted by gender, age, diabetes duration, body mass index, systolic blood pressure, HbA1c, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, and alcohol intake.

[b] One drink is equivalent to 12.6 g ethanol based on the U.S. Department of Agriculture definition.

lowering levels of LDL cholesterol is given priority over that of triglycerides in most current guidelines for diabetes (22), more attention toward triglycerides should be given in East Asians with diabetes. In contrast to the favorable results of statin trials, fibrates, which mainly lower triglyceride levels, failed to significantly reduce cardiovascular events in diabetic subjects (23). However, this study mostly involved White subjects; therefore, the effects of lowering triglycerides in East Asians with diabetes are still to be determined.

Details of the etiology and pathological mechanisms for the stronger association of serum triglyceride levels with CHD in diabetic subjects in East Asia than in Western countries cannot be fully elucidated from results of the epidemiological studies discussed above. Although triglycerides *per se* do not seem to be directly involved in the atherogenic process, its conjunction with small dense LDL or remnant particles based on insulin-resistant status, which are important accelerators of atherosclerosis in diabetes, is well known (21). However, because we did not measure the small dense LDL, remnant particles, or fasting insulin levels to determine the degree of insulin resistance, we cannot address their role among our study subjects. It was reported in Japanese subjects with type 2 diabetes that the serum triglyceride level is associated with insulin resistance, the visceral fat area (24) and C-reactive protein

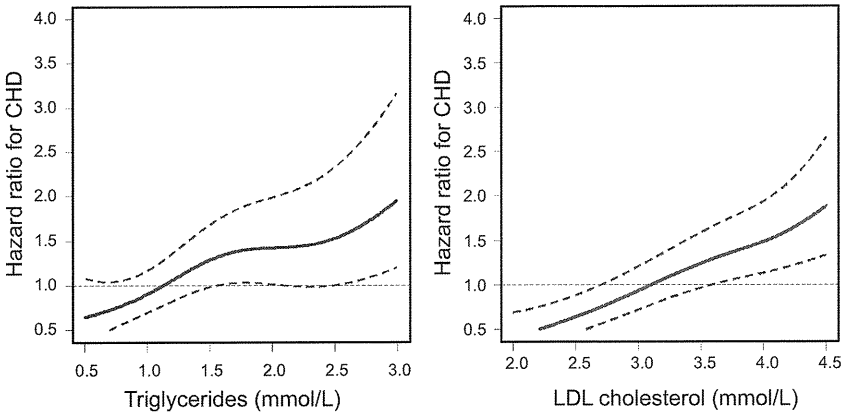


**FIG. 1.** Spline curves of HR with 95% CI showing relationships between major risk factors and CHD events estimated by generalized additive models.

(25). A prospective study showed that the triglyceride value was a strong predictor of recurrent coronary events in patients with relatively low LDL cholesterol (26). Because more than one fourth of our subjects were taking agents for dyslipidemia, many of which were statins that lower LDL cholesterol, the significance of triglycerides as a predictor of CHD could be exaggerated.

It should be noted that the high-density lipoprotein (HDL) cholesterol level, which has a negative correlation with the triglyceride level, was not a significant predictor for CHD in our cohort after multivariate adjustment, although in the UKPDS (18), low HDL cholesterol values were the second strongest predictor for CHD after LDL cholesterol, and the triglyceride value was not an independent predictor after multivariate adjustment. It is already known (27, 28), and was actually observed in our cohort, that the serum level of HDL cholesterol is naturally higher in East Asians than in Western populations. Therefore, it could be possible that the influence of HDL cholesterol was not apparent, and instead, that of triglycerides was enhanced in Japanese. Another possibility was that when two explanatory variables with significant correlations, as in the case of HDL cholesterol and triglycerides, were in a regression model, the stronger and more precisely measured factor had significance, and the other seemed to be absorbed. Our findings are consistent with other studies of a Japanese general population (29, 30) that showed triglycerides as an independent risk factor not substantially influenced by total or HDL cholesterol.

Moderate alcohol intake is known to increase both triglyceride and HDL cholesterol levels and reduces CHD. Therefore, the expected effects of ethanol would not likely account for adverse association of elevated triglyceride levels with elevated CHD risk, and ethanol intake would also not likely account for the lack of expected inverse association between HDL cholesterol levels and CHD in this study. It could be possible that the low intake of ethanol in the study population might explain the lack of the expected ethanol effects.

Our results also imply that the triglyceride level seemed to have affected CHD risk possibly in an additive fashion to the LDL cholesterol level (although not statistically significant) despite the fact that it worked independently of blood pressure. Even among subjects in the top tertile of either triglyceride or LDL cholesterol values, only those in whom the rest of these lipid variables were in the middle or the top tertile were at significantly higher risk compared with those who were in the lowest tertiles of both of these variables. Although it is not known whether this phenomenon can be seen in diabetic subjects of other ethnicities, its mechanism requires investigation.

The significant elevation of baseline proportions of those receiving therapy with antihypertensive agents or biguanides among subjects with cardiovascular events should be carefully interpreted. It is not rare that in observational studies the use of drug therapy is associated with worse cardiovascular outcome because of so-called indication bias or treatment selection bias (31, 32). Therefore, the possible reason for this contradictory result is that patients who originally had a higher cardiovascular risk tended to be prescribed these agents, which had been proved to have antiatherogenic effects in clinical trials (33, 34), because our patients were cared by diabetes specialists.

A markedly lower incidence of CHD compared with Western diabetic populations was confirmed in our Japanese subjects. The incidence of myocardial infarction in our cohort was approximately one fourth of that reported in the United Kingdom (35, 36), whereas the incidence of stroke was quite similar (35, 37). In addition, the current finding that stroke is more frequent than myocardial infarction in Japanese subjects with diabetes, which is the reverse of that in other ethnic groups (2), is a reflection of the same relationship that has been observed in the Japanese general population (38). In terms of risk factors for stroke, as was seen in Western diabetic subjects (37, 39), blood pressure was confirmed to be a leading predictor of stroke. This strong correlation, which is universally seen beyond ethnic groups, might have concealed the relationship between stroke and lipid variables including triglycerides, which was prominent in CHD.

The strengths of this study lie in its long-term prospective design of a nation-representative cohort consisting of patients from a large number of institutions throughout

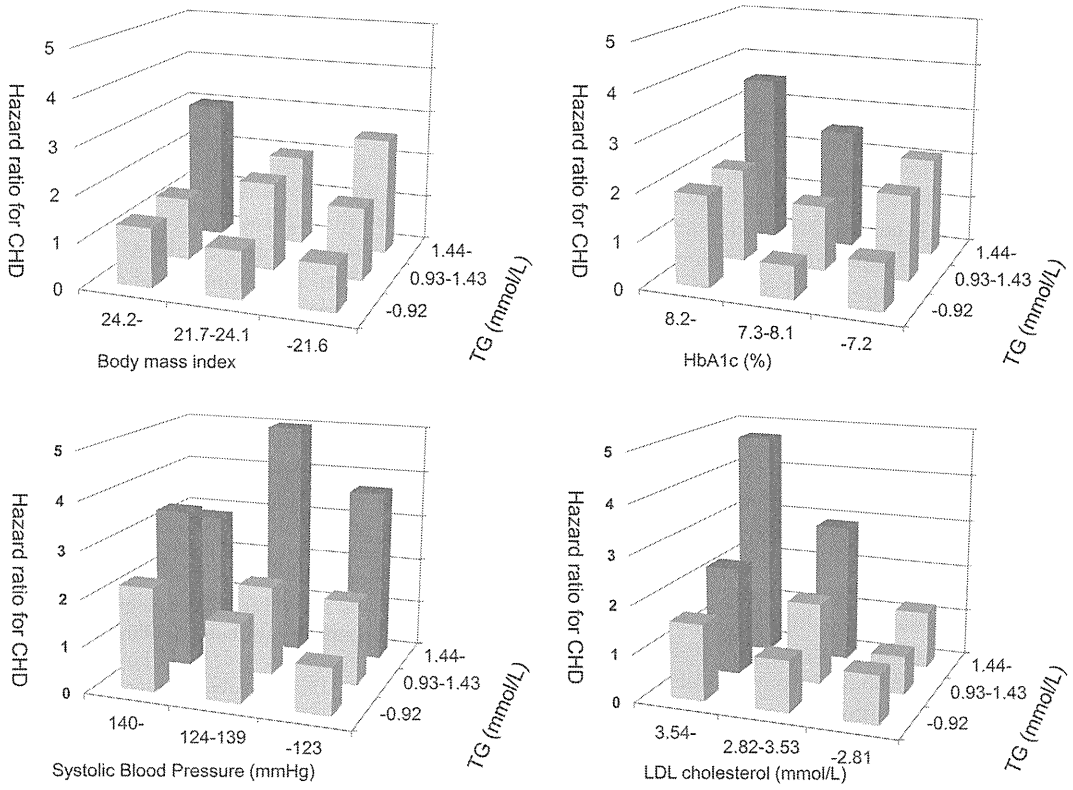


**FIG. 2.** Combined roles of triglycerides (TG) with other major risk factors for CHD. Each variable was stratified according to tertiles. Columns of categories with a significantly elevated HR compared with the reference category, which is the combination of the lowest tertiles of both parameters for each combination, are shown by *dark shading*.

Japan. However, the number of patients was not necessarily large enough to draw firm conclusions, and our patients comprised only Japanese recruited from clinics specializing in diabetes care. Therefore, our results may not be representative of all East Asians. A limitation was the lack of standardization in measurement methods for laboratory testing, although in Japan, laboratory tests are well standardized on a nationwide level. Another limitation was that we could not detect asymptomatic angina pectoris, which could possibly occur in diabetic subjects, although asymptomatic myocardial infarctions were detected by an annual ECG.

In conclusion, an elevated triglyceride level was a strong predictor for CHD in Japanese subjects with type 2 diabetes, which implies that more therapeutic attention toward serum triglycerides should be given in Japanese with diabetes. These results could be crucial in ethnic group-specific diabetes care and could also highlight the clinical background in the development of cardiovascular complications in patients with diabetes.

## Appendix

The Japan Diabetes Complications Study (JDCS) Group (including current and former members with their affiliations at the time of their participation in this study) includes primary investigators Hirohito Sone and Nobuhio Yamada (University of Tsukuba) and Chief in Assessment Committee Yasuo Akanuma (Institute for Adult Diseases Asahi Life Foundation).

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All authors researched data, contributed to the discussion, and wrote and edited the manuscript. H.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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# $HbA_{1c}$ 5·7–6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study

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## Summary

**Background** **The clinical relevance of the diagnostic criteria for prediabetes to prediction of progression to diabetes has been little studied. We aimed to compare the prevalence of prediabetes when assessed by the new glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) 5·7–6·4% criterion or by impaired fasting glucose, and assessed differences in progression rate to diabetes between these two criteria for prediabetes in a Japanese population.**

**Methods** **Our longitudinal cohort study included 4670 men and 1571 women aged 24–82 years without diabetes at baseline (diabetes was defined as fasting plasma glucose ≥7·0 mmol/L, self-reported clinician-diagnosed diabetes, or $HbA_{1c}$ ≥6·5%) who attended Toranomon Hospital (Tokyo, Japan) for a routine health check between 1997 and 2003. Participants with a baseline diagnosis of prediabetes according to impaired fasting glucose (fasting plasma glucose 5·6–6·9 mmol/L) or $HbA_{1c}$ 5·7–6·4%, or both, were divided into four groups on the basis of baseline diagnosis of prediabetes. Rate of progression to diabetes was assessed annually.**

**Findings** **Mean follow-up was 4·7 (SD 0·7) years. 412 (7%) of 6241 participants were diagnosed with prediabetes on the basis of the $HbA_{1c}$ 5·7–6·4% criterion. Screening by $HbA_{1c}$ alone missed 1270 (61%) of the 2092 prediabetic individuals diagnosed by a combination of impaired fasting glucose and $HbA_{1c}$ 5·7–6·4%. Overall cumulative probability of progression to diabetes did not differ significantly between participants with prediabetes discordantly diagnosed by either $HbA_{1c}$ or impaired fasting glucose alone (incidence was 7% for $HbA_{1c}$ alone [n=412 individuals and 30 incident cases] and 9% for impaired fasting glucose alone [n=1270, 108 cases]; log-rank test, p=0·3317). Multivariate-adjusted hazard ratios for incident diabetes were 6·16 (95% CI 4·33–8·77) for those diagnosed with prediabetes by impaired fasting glucose alone and 6·00 (3·76–9·56) for diagnosis by $HbA_{1c}$ alone, and were substantially increased to 31·9 (22·6–45·0) for diagnosis by both impaired fasting glucose and $HbA_{1c}$ compared with normoglycaemic individuals.**

**Interpretation** **Diagnosis of prediabetes by both the new $HbA_{1c}$ criterion and impaired fasting glucose identified individuals with an increased risk of progression to diabetes. Although the new $HbA_{1c}$ criterion identified fewer individuals at high risk than did impaired fasting glucose, the predictive value for progression to diabetes assessed by $HbA_{1c}$ 5·7–6·4% was similar to that assessed by impaired fasting glucose alone. The two tests used together could efficiently target people who are most likely to develop diabetes and allow for early intervention.**

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## Introduction

In prediabetes, blood glucose concentrations are higher than normal, but are not high enough for diagnosis of diabetes. The disorder is thought to place individuals at high risk of future diabetes, according to the American Diabetes Association (ADA).[1] ADA guidelines suggest targeting of individuals identified as having prediabetes for early intervention.[1] A new criterion has been proposed for the diagnosis of prediabetes: glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) 5·7–6·4%. However, the performance of $HbA_{1c}$ as a screening test for identification of prediabetic individuals has been controversial.[2–6] Many individuals who were diagnosed as having prediabetes on the basis of impaired fasting glucose are reclassified as not having the disorder when the new $HbA_{1c}$ 5·7–6·4% criterion is used; thus, screening by $HbA_{1c}$ alone might miss a large number of prediabetic individuals.[2–5] The new criterion's performance in detection of prediabetic individuals differs according to ethnic origin,[4,5] and more evidence of its usefulness in non-western populations is needed.[4,6]

Few studies[7,8] have longitudinally compared the difference in progression rate to diabetes after diagnosis of prediabetes with the $HbA_{1c}$ 5·7–6·4% criterion or by impaired fasting glucose, or established which criterion for prediabetes is clinically relevant for prediction of progression. Whether introduction of the new $HbA_{1c}$ criterion in addition to assessment of fasting glucose could efficiently target prediabetic individuals who are most likely to progress to diabetes is unclear. We aimed to evaluate the effect of introduction of the $HbA_{1c}$ 5·7–6·4% criterion into diagnosis of prediabetes by

impaired fasting glucose, and to longitudinally assess differences in the progression rate to diabetes between individuals diagnosed with prediabetes on the basis of these two criteria in a large Japanese cohort. We tested whether the two tests used together could target people most likely to progress to diabetes, which would allow early intervention.

| | Study participants (n=6241) |
|---|---|
| Age (years) | 49·9 (8·7) |
| Men | 4670 (75%) |
| Smoking habit | |
| Never | 3342 (54%) |
| Former | 1503 (24%) |
| Current | 1396 (22%) |
| BMI ≥25·0 kg/m² | 1215 (19%) |
| Hypertension | 1320 (21%) |
| Dyslipidaemia | 1962 (31%) |
| History of coronary heart disease | 84 (1%) |
| History of stroke | 16 (<1%) |

Data are n (%) or mean (SD). Hypertension is defined as systolic blood pressure 140 mm Hg or higher, diastolic blood pressure 90 mm Hg or higher, or on treatment. Dyslipidaemia is defined as triglyceride concentration 1·7 mmol/L or higher, HDL cholesterol lower than 1·03 mmol/L, or on treatment. BMI=body-mass index.

*Table 1:* Overall baseline characteristics

## Methods

### Study population

The Toranomon Hospital Health Management Center Study (TOPICS) included a cohort consisting mainly of apparently healthy Japanese government employees who underwent annual examinations for health screening. The details of the study have been described previously.[9] The cohort consisted of 32 057 individuals who had a routine health check for the first time between 1997 and 2003 at the Health Management Center, Toranomon Hospital (Tokyo, Japan). Of these 32 057 individuals, our investigation included 6636 individuals who had annual examinations regularly for 4 years (n=1716) or 5 years (n=4920) after the initial examination. Registered nurses interviewed all participants at the time of each annual examination using standard questionnaires that gathered information about demographic characteristics, medical history, and health-related habits. We excluded 310 individuals who had diabetes at the baseline examination (192 individuals were previously diagnosed and 118 were undiagnosed) or who had missing data for baseline characteristics (n=89). Subsequently, 6241 individuals aged 24–82 years were eligible for our analysis.

The study protocol was consistent with the Japanese Government's ethics guidelines regarding epidemiological studies in accordance with the Declaration of Helsinki and was reviewed by the institutional review

| | | Prediabetes | | | p value | | |
|---|---|---|---|---|---|---|---|
| | Normoglycaemia (group 1, n=4149) | IFG alone (group 2, n=1270) | $HbA_{1c}$ 5·7–6·4% alone (group 3, n=412) | Both $HbA_{1c}$ 5·7–6·4% and IFG (group 4, n=410) | 1 vs 2 | 1 vs 3 | 1 vs 4 |
| Age (years) | 49·2 (48·9–49·4) | 49·9 (49·5–50·4) | 54·3 (53·5–55·1) | 53·7 (52·8–54·5) | 0·0048 | <0·0001 | <0·0001 |
| Women | 1252 (30%) | 118 (9%) | 130 (32%) | 71 (17%) | <0·0001 | 0·56 | <0·0001 |
| Family history of diabetes | 532 (13%) | 194 (15%) | 69 (17%) | 90 (22%) | 0·0247 | 0·0247 | <0·0001 |
| Current smoking | 880 (21%) | 312 (25%) | 101 (25%) | 103 (25%) | 0·0115 | 0·12 | 0·0661 |
| BMI (kg/m²)* | 22·5 (22·4–22·6) | 23·5 (23·3–23·6) | 22·9 (22·7–23·2) | 23·8 (23·6–24·1) | <0·0001 | 0·0034 | <0·0001 |
| Obesity (BMI ≥25·0 kg/m²)* | 648 (16%) | 370 (29%) | 73 (18%) | 124 (30%) | <0·0001 | 0·27 | <0·0001 |
| Systolic blood pressure (mm Hg)* | 123 (123–124) | 130 (129–131) | 123 (121–124) | 127 (126–129) | <0·0001 | 0·52 | <0·0001 |
| Diastolic blood pressure (mm Hg)* | 75 (75–76) | 80 (80–81) | 75 (74–76) | 78 (77–79) | <0·0001 | 0·37 | <0·0001 |
| Triglycerides (mmol/L)* | 1·23 (1·21–1·26) | 1·43 (1·38–1·47) | 1·33 (1·25–1·41) | 1·59 (1·51–1·67) | <0·0001 | 0·0179 | <0·0001 |
| Total cholesterol (mmol/L)* | 5·22 (5·19–5·24) | 5·37 (5·33–5·42) | 5·35 (5·27–5·43) | 5·46 (5·38–5·54) | <0·0001 | 0·0015 | <0·0001 |
| HDL cholesterol (mmol/L)* | 1·41 (1·40–1·42) | 1·42 (1·40–1·44) | 1·33 (1·29–1·36) | 1·31 (1·28–1·34) | 0·49 | <0·0001 | <0·0001 |
| γ-glutamyltransferase (units per L)* | 46·1 (44·5–47·8) | 63·8 (60·8–66·8) | 50·3 (45·0–55·5) | 65·0 (59·7–70·3) | <0·0001 | 0·14 | <0·0001 |
| Uric acid (μmol/L)* | 333·7 (331·6–335·8) | 349·1 (345·3–352·9) | 334·5 (327·8–341·2) | 354·9 (348·2–361·6) | <0·0001 | 0·83 | <0·0001 |
| eGFR (ml/min per 1·73m²)* | 75·5 (75·1–75·8) | 76·2 (75·6–76·9) | 74·5 (73·3–75·6) | 75·9 (74·7–77·1) | 0·0559 | 0·11 | 0·50 |
| White cell count (×10⁹/L)* | 5·2 (5·2–5·3) | 5·3 (5·2–5·4) | 5·5 (5·4–5·7) | 5·6 (5·5–5·8) | 0·0654 | 0·0001 | <0·0001 |
| Haemoglobin (g/L)* | 145 (144–145) | 146 (146–147) | 141 (140–142) | 145 (144–146) | <0·0001 | <0·0001 | 0·18 |
| Fasting plasma glucose (mmol/L)* | 5·1 (5·0–5·1) | 5·8 (5·8–5·8) | 5·1 (5·1–5·2) | 6·0 (6·0–6·0) | <0·0001 | <0·0001 | <0·0001 |
| $HbA_{1c}$ (%)* | 5·2% (5·2–5·2) | 5·3% (5·3–5·3) | 5·8% (5·8–5·8) | 5·9% (5·8–5·9) | <0·0001 | <0·0001 | <0·0001 |

Data are n (%) or mean (95% CI). Categorical data were analysed with the $\chi^2$ test. $HbA_{1c}$ was estimated as the National Glycohemoglobin Standardization Program equivalent value (%). Normoglycaemia was defined as $HbA_{1c}$ less than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when $HbA_{1c}$ less than 5·7% and FPG 5·6–6·9 mmol/L, by $HbA_{1c}$ alone when $HbA_{1c}$ 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both $HbA_{1c}$ and IFG when $HbA_{1c}$ 5·7–6·4% and FPG 5·6–6·9 mmol/L. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. IFG=impaired fasting glucose. FPG=fasting plasma glucose. BMI=body-mass index. eGFR=estimated glomerular filtration rate. *Adjusted for age and sex.

*Table 2:* Baseline characteristics according to diagnosis of prediabetes by $HbA_{1c}$ and IFG criteria

board at Toranomon Hospital. Written informed consent was obtained from all participants.

### Procedures

Blood samples were obtained after an overnight fast (12 h) and tested with an automatic clinical chemistry analyser (Hitachi, LABOSPECT 008, Tokyo, Japan). Blood glucose, serum triglyceride, total cholesterol, HDL cholesterol, and uric acid concentrations were measured by enzymatic methods. $HbA_{1c}$ was assessed by high-performance liquid chromatography. The intra-assay coefficient of variation was 0·7% with a mean of 4·29%, and the interassay coefficient of variation was 0·7% with a mean of 4·29%. The value for $HbA_{1c}$ was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the formula:[10]

$$HbA_{1c}\,(\%) = HbA_{1c}\,(\text{Japan Diabetes Society})\,(\%) + 0{\cdot}4\%$$

Diabetes was defined in accordance with ADA guidelines[1] as a fasting plasma glucose (FPG) concentration of 7·0 mmol/L or higher, self-reported clinician-diagnosed diabetes, or $HbA_{1c}$ 6·5% or higher. Baseline diagnosis of prediabetes was based on the new ADA criterion[1] of impaired fasting glucose (FPG 5·6–6·9 mmol/L) or $HbA_{1c}$ 5·7–6·4%, or both. Participants were divided into four groups on the basis of baseline diagnosis of prediabetes: (1) normoglycaemia ($HbA_{1c}$ <5·7% and FPG <5·6 mmol/L); (2) impaired fasting glucose alone ($HbA_{1c}$ <5·7% and FPG 5·6–6·9 mmol/L); (3) $HbA_{1c}$ 5·7–6·4% alone ($HbA_{1c}$ 5·7–6·4% and FPG <5·6 mmol/L); and (4) both $HbA_{1c}$ 5·7–6·4% and impaired fasting glucose ($HbA_{1c}$ 5·7–6·4% and FPG 5·6–6·9 mmol/L). Additionally, to investigate whether similar associations between a baseline diagnosis of prediabetes and future risk of diabetes would be identified irrespective of the diagnostic criteria for incident diabetes, we did an analysis of incident cases of diabetes that were diagnosed with three other criteria: diabetes indicated by self-reported clinician-diagnosis; diabetes indicated by self-reported clinician-diagnosis or FPG 7·0 mmol/L or higher; or diabetes indicated by self-reported clinician-diagnosis or $HbA_{1c}$ 6·5% or higher.

### Statistical analysis

We used SPSS (version 16.0) for all analyses and regarded p values lower than 0·05 as significant. We compared baseline characteristics between the four prediabetic groups using a general linear model with adjustments for age and sex. The level of agreement of the diagnostic categories between FPG and $HbA_{1c}$ criteria was examined with κ statistics.[11] The diagnostic property of $HbA_{1c}$ for FPG 5·6–6·9 mmol/L was cross-sectionally evaluated by a receiver operating characteristic (ROC) curve. We also did an analysis when FPG concentrations of

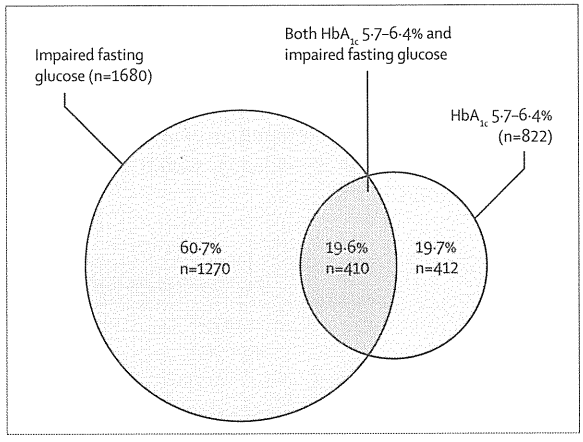


*Figure 1:* **Prevalence of individuals with prediabetes according to diagnosis by glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) 5·7–6·4% and impaired fasting glucose (fasting plasma glucose 5·6–6·9 mmol/L) criteria at a baseline examination (n=2092)**

| | Proportion of total population (%) | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|---|
| 6·4% | <1% | 1% | 100% | 100% | 73% |
| 6·3% | <1% | 1% | 100% | 89% | 73% |
| 6·2% | 1% | 3% | 100% | 79% | 74% |
| 6·1% | 2% | 5% | 99% | 72% | 74% |
| 6·0% | 3% | 8% | 99% | 67% | 74% |
| 5·9% | 5% | 12% | 97% | 59% | 75% |
| 5·8% | 8% | 17% | 95% | 54% | 76% |
| 5·7% | 13% | 24% | 91% | 50% | 77% |
| 5·6% | 21% | 35% | 85% | 46% | 78% |
| 5·5% | 30% | 46% | 76% | 42% | 79% |
| 5·4% | 41% | 57% | 65% | 37% | 80% |
| 5·3% | 53% | 69% | 52% | 35% | 82% |
| 5·2% | 66% | 79% | 40% | 33% | 84% |

Impaired fasting glucose was defined as fasting plasma glucose 5·6–6·9 mmol/L. $HbA_{1c}$=glycated haemoglobin $A_{1c}$.

*Table 3:* **Sensitivity, specificity, and positive and negative predictive values for identification of individuals with impaired fasting glucose at different $HbA_{1c}$ thresholds**

| | Participants without diabetes (n=5903) | Participants with diabetes (n=338) |
|---|---|---|
| Normoglycaemia | 4103 (70%) | 46 (14%) |
| Baseline diagnosis of prediabetes | | |
| IFG alone | 1162 (20%) | 108 (32%) |
| $HbA_{1c}$ 5·7–6·4% alone | 382 (6%) | 30 (9%) |
| Both $HbA_{1c}$ 5·7–6·4% and IFG | 256 (4%) | 154 (46%) |

Data are n (%). Normoglycaemia was defined as $HbA_{1c}$ lower than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when $HbA_{1c}$ lower than 5·7% and FPG 5·6–6·9 mmol/L, by $HbA_{1c}$ alone when $HbA_{1c}$ 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both $HbA_{1c}$ and IFG when $HbA_{1c}$ 5·7–6·4% and FPG 5·6–6·9 mmol/L. IFG=impaired fasting glucose. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. FPG=fasting plasma glucose.

*Table 4:* **Comparison of baseline diagnosis of prediabetes between individuals who did and did not develop type 2 diabetes**

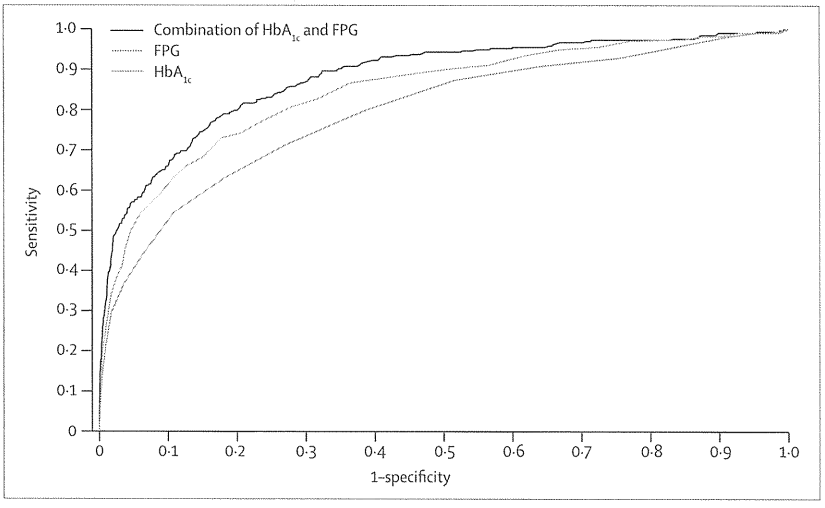


*Figure 2:* **ROC curve for prediction of future diabetes by $HbA_{1c}$, by FPG, and by the combination of $HbA_{1c}$ and FPG**
ROC curve for $HbA_{1c}$, AUC 0·795 (95% CI 0·767–0·822); ROC curve for FPG, AUC 0·846 (0·821–0·870); ROC curve for the combination of $HbA_{1c}$ and FPG, AUC 0·880 (0·859–0·901). ROC=receiver operating characteristic. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. FPG=fasting plasma glucose. AUC=area under the curve.

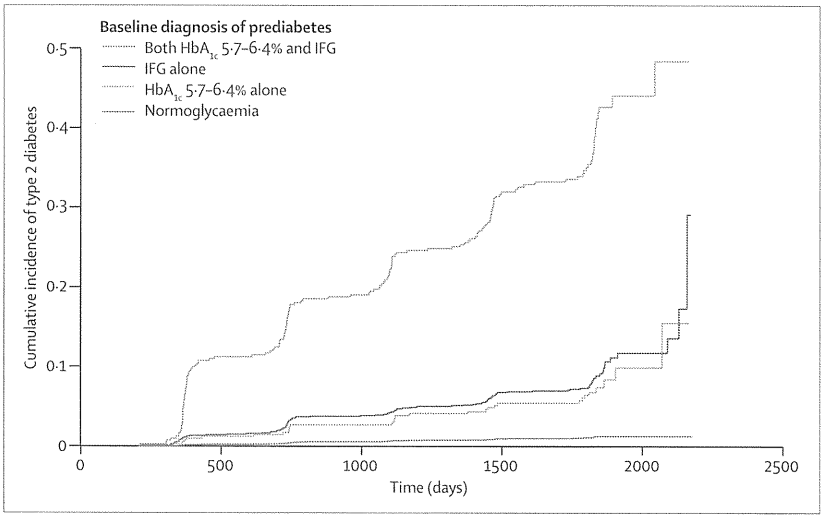


*Figure 3:* **Cumulative incidence of diabetes during follow-up according to baseline diagnosis of prediabetes**
Log-rank test, p=0·3317 between IFG alone and $HbA_{1c}$ 5·7–6·4% alone. Normoglycaemia defined as $HbA_{1c}$ lower than 5·7% and FPG lower than 5·6 mmol/L. Diagnosis of prediabetes by IFG alone defined as $HbA_{1c}$ less than 5·7% and FPG 5·6–6·9 mmol/L, by $HbA_{1c}$ alone defined as $HbA_{1c}$ 5·7–6·4% and FPG lower than 5·6 mmol/L, and by both $HbA_{1c}$ and IFG defined as $HbA_{1c}$ 5·7–6·4% and FPG 5·6–6·9 mmol/L. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. IFG=impaired fasting glucose. FPG=fasting plasma glucose.

6·1–6·9 mmol/L rather than 5·6–6·9 mmol/L were applied as the reference criterion.

In prospective analyses, we undertook an ROC analysis for prediction of risk of future diabetes on the basis of $HbA_{1c}$, FPG, and the combination of the two values ($HbA_{1c}$ and FPG). Risk established for the combination of the two tests was calculated as: log hazard ratio = (β1×FPG) + (β2×$HbA_{1c}$). Unadjusted overall time to the development of diabetes was described by Kaplan-Meier analysis with log-rank testing. Cox regression was used to estimate the hazard ratios (HRs) and their 95% CIs for each baseline diagnosis of prediabetes with a normoglycaemic group as the reference. Follow-up for each participant was calculated from the date of the first examination to the date of confirmed diabetes or the date of the last follow-up examination.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Prevalence of diabetes in the entire study population was 5% (1684 of 32 057 people). Table 1 shows characteristics of study participants (n=6241). On the basis of the $HbA_{1c}$ 5·7–6·4% criterion, 412 (7%) individuals in the study population had newly diagnosed prediabetes (table 2). Prediabetic individuals diagnosed by impaired fasting glucose but not by $HbA_{1c}$ had significantly different characteristics at the baseline examination compared with those diagnosed by $HbA_{1c}$ but not by fasting glucose. Those diagnosed on the basis of $HbA_{1c}$ alone were more likely to be women, older, and less hypertensive, to have a lower body-mass index (BMI), lower triglyceride, uric acid, HDL cholesterol, and γ-glutamyltransferase concentrations, and higher leucocyte counts than those diagnosed by impaired fasting glucose alone (adjusted for age and sex).

Of 2092 prediabetic individuals at the baseline examination, only 20% (n=412) were classified as having prediabetes by the $HbA_{1c}$ criterion without impaired fasting glucose (figure 1). Screening by $HbA_{1c}$ alone missed 61% of the total number of prediabetic individuals diagnosed by a combination of impaired fasting glucose and $HbA_{1c}$ 5·7–6·4%, and 1270 prediabetic individuals previously diagnosed by impaired fasting glucose (n=1680) were not classified as having prediabetes. The magnitude of overlap between the two criteria was low: 50% of prediabetic individuals diagnosed by $HbA_{1c}$ also had impaired fasting glucose (n=410/822), and 24% of those diagnosed by impaired fasting glucose also had $HbA_{1c}$ 5·7–6·4% (n=410/1680). We noted poor agreement between impaired fasting glucose and $HbA_{1c}$ criteria (κ 0·18, 95% CI 0·16–0·21). $HbA_{1c}$ ranging between 5·6% and 6·4% provided the highest agreement with impaired fasting glucose (κ 0·22, 0·19–0·24), although the improvement was small.

The area under the curve for the ROC analysis with $HbA_{1c}$ for diagnosis of prediabetes by impaired fasting glucose was 0·656 (95% CI 0·641–0·672). For identification of individuals with impaired fasting glucose, a threshold of $HbA_{1c}$ 5·7% showed high specificity of 91% and low sensitivity of 24%, wher eas $HbA_{1c}$ 5·5% gave the highest combination of specificity (76%) and sensitivity (46%; table 3). When the more restrictive definition for impaired fasting glucose of FPG 6·1–6·9 mmol/L was

applied instead of 5·6–6·9 mmol/L, the prevalence of prediabetes by impaired fasting glucose decreased from 27% (n=1680) to 6% (n=380) among the total population, and 17% (n=1043) had prediabetes by either FPG 6·1–6·9 mmol/L or $HbA_{1c}$ 5·7–6·4%. The area under the curve for the ROC analysis with $HbA_{1c}$ for detection of FPG 6·1–6·9 mmol/L was 0·740 (95% CI 0·714–0·766), and the threshold of $HbA_{1c}$ 5·7% showed a sensitivity of 42% and specificity of 89%.

After the baseline diagnosis of prediabetes, we documented 338 incident cases of diabetes during a mean 4·7 years' (SD 0·7) annual follow-up. A prediabetic state assessed by impaired fasting glucose alone, by $HbA_{1c}$ 5·7–6·4% alone, or by both fasting glucose and $HbA_{1c}$ preceded diabetes in 32% (n=108), 9% (n=30), and 46% (n=154) of incident cases of diabetes, respectively (table 4). Of the incident cases, 86% (n=292) were predicted by either impaired fasting glucose or $HbA_{1c}$ 5·7–6·4%, whereas 14% (n=46) with normoglycaemia at baseline progressed straight to diabetes. Among normoglycaemic individuals ($HbA_{1c}$ <5·7% and FPG <5·6 mmol/L), higher baseline levels of both $HbA_{1c}$ and FPG, even though within a normal range, were associated with development of diabetes. As to age-adjusted and sex-adjusted HRs, for each 0·5% increase in $HbA_{1c}$ there was a 2·57 (95% CI 1·32–5·00) increase in the HR and for each 0·55 mmol/L (10 mg/dl) increase in FPG values there was an increase of 2·33 (95% CI 1·19–4·57) in the HR.

The ROC curve plot for prediction of future diabetes by $HbA_{1c}$, by FPG, or by the combination of the two tests showed that the combination of FPG and $HbA_{1c}$ slightly but significantly ($p<0·0001$) improved the area under the curve for prediction of future diabetes compared with use of only one test for screening (figure 2).

Figure 3 shows a Kaplan-Meier survival curve for prediction of diabetes after a baseline diagnosis of prediabetes. Incidence was 7% for $HbA_{1c}$ alone (n=412 individuals and 30 incident cases) and 9% for impaired fasting glucose alone (n=1270, 108 incident cases). Overall cumulative probability did not differ significantly between the two (log-rank test, p=0·3317). Of prediabetic individuals who fulfilled both $HbA_{1c}$ and fasting glucose criteria at baseline, 38% (n=154) progressed to diabetes within 5 years. If a definition for impaired fasting glucose of FPG 6·1–6·9 mmol/L was applied rather than FPG 5·6–6·9 mmol/L, incidence was 2% for $HbA_{1c}$ lower than 5·7% and FPG lower than 6·1 mmol/L (n=5198 individuals and 100 incident cases). With $HbA_{1c}$ alone, FPG alone, and both FPG and

| | Total (n=6241) | Normoglycaemia (n=4149) | Prediabetes | | |
|---|---|---|---|---|---|
| | | | IFG alone (n=1270) | $HbA_{1c}$ 5·7–6·4% alone (n=412) | Both $HbA_{1c}$ 5·7–6·4% and IFG (n=410) |
| **Incidence of diabetes by self-reported clinician diagnosis** | | | | | |
| Incident cases/person-years | 157/29 856 | 34/19 982 | 43/6029 | 14/1985 | 66/1860 |
| Incident rate (per 1000 person-years) | 5·3 | 1·7 | 7·1 | 7·1 | 35·5 |
| Age-adjusted and sex-adjusted hazard ratio (95% CI) | .. | 1·00 | 3·53 (2·24–5·55) | 3·68 (1·96–6·91) | 17·4 (11·4–26·6) |
| Multivariate hazard ratio (95% CI) | .. | 1·00 | 3·40 (2·14–5·39) | 3·48 (1·85–6·54) | 15·8 (10·2–24·6) |
| **Incidence of diabetes by self-reported clinician diagnosis or $HbA_{1c}$ ≥6·5%** | | | | | |
| Incident cases/person-years | 250/29 684 | 39/19 973 | 62/6006 | 26/1968 | 123/1737 |
| Incident rate (per 1000 person-years) | 8·4 | 2·0 | 10·3 | 13·2 | 70·8 |
| Age-adjusted and sex-adjusted hazard ratio (95% CI) | .. | 1·00 | 4·54 (3·03–6·79) | 6·63 (4·02–11·0) | 33·8 (23·4–48·8) |
| Multivariate hazard ratio (95% CI) | .. | 1·00 | 4·34 (2·88–6·54) | 6·24 (3·77–10·3) | 30·5 (20·9–44·6) |
| **Incidence of diabetes by self-reported clinician diagnosis or FPG ≥7·0 mmol/L** | | | | | |
| Incident cases/person-years | 298/29 558 | 43/19 965 | 101/5927 | 21/1978 | 133/1688 |
| Incident rate (per 1000 person-years) | 10·1 | 2·2 | 17·0 | 10·6 | 78·8 |
| Age-adjusted and sex-adjusted hazard ratio (95% CI) | .. | 1·00 | 6·77 (4·73–9·7) | 4·83 (2·85–8·17) | 33·8 (23·8–47·9) |
| Multivariate hazard ratio (95% CI) | .. | 1·00 | 6·00 (4·16–8·6) | 4·34 (2·56–7·35) | 26·8 (18·7–38·4) |
| **Incidence of diabetes by self-reported clinician diagnosis, $HbA_{1c}$ ≥6·5% or FPG ≥7·0 mmol/L** | | | | | |
| Incident cases/person-years | 338/29 487 | 46/19 961 | 108/5920 | 30/1965 | 154/1641 |
| Incident rate (per 1000 person-years) | 11·5 | 2·3 | 18·2 | 15·3 | 93·8 |
| Age-adjusted and sex-adjusted hazard ratio (95% CI) | .. | 1·00 | 6·86 (4·84–9·71) | 6·53 (4·10–10·4) | 38·6 (27·6–54·0) |
| Multivariate hazard ratio (95% CI) | .. | 1·00 | 6·16 (4·33–8·77) | 6·00 (3·76–9·56) | 31·9 (22·6–45·0) |

Normoglycaemia was defined as $HbA_{1c}$ lower than 5·7% and FPG less than 5·6 mmol/L. Diagnosis of prediabetes was by IFG alone when $HbA_{1c}$ less than 5·7% and FPG 5·6–6·9 mmol/L, by $HbA_{1c}$ alone when $HbA_{1c}$ 5·7–6·4% and FPG less than 5·6 mmol/L, and by both $HbA_{1c}$ and IFG when $HbA_{1c}$ 5·7–6·4% and FPG 5·6–6·9 mmol/L. Multivariate model was adjusted for age, sex, smoking habit (never/former/current), parental history of diabetes, body-mass index, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or treatment), HDL cholesterol, log-transformed triglycerides, and γ-glutamyltransferase. IFG=impaired fasting glucose. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. FPG=fasting plasma glucose.

*Table 5:* **Hazard ratios for development of type 2 diabetes according to baseline diagnosis of prediabetes**

$HbA_{1c}$, incidence rates were 13% (n=663 individuals and 83 incident cases), 24% (n=221, 54 cases), and 64% (n=159, 101 cases), respectively (log-rank test, p<0·0001).

Results of Cox analysis showed that the HR for incident diabetes was similarly increased for individuals with prediabetes discordantly diagnosed by either $HbA_{1c}$ or fasting glucose criteria alone (table 5). The age-adjusted and sex-adjusted HR was 6·86 (95% CI 4·84–9·71) in those diagnosed with prediabetes by impaired fasting glucose alone and 6·53 (4·10–10·4) for those diagnosed with prediabetes on the basis of $HbA_{1c}$ alone compared with normoglycaemic individuals. However, prediabetic individuals who fulfilled both criteria had a substantially increased risk, with an HR of 38·6 (95% CI 27·6–54·0). Although further adjustments for a parental history of diabetes, smoking habit (never, former, or current smokers), BMI, hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both, or treatment), γ-glutamyltransferase, HDL cholesterol, and log-transformed triglycerides attenuated the HRs, the results were fundamentally the same.

Multivariate-adjusted HRs for impaired fasting glucose alone, $HbA_{1c}$ 5·7–6·4% alone, and both $HbA_{1c}$ and impaired fasting glucose were 6·16 (95% CI 4·33–8·77), 6·00 (3·76–9·56), and 31·9 (22·6–45·0), respectively. We noted similar associations irrespective of the diagnostic criteria for incident diabetes (table 5). The association of a diagnosis of prediabetes and risk of diabetes was fundamentally the same irrespective of the presence of anaemia, obesity, or becoming obese at follow-up (data not shown).

## Discussion

This study showed that diagnosis of prediabetes by both new $HbA_{1c}$ and fasting glucose criteria identified individuals in a Japanese population at a substantially increased risk for progression to diabetes within 5 years. Although the new $HbA_{1c}$ criterion identified fewer participants at high risk than were identified by impaired fasting glucose, the predictive value for progression to diabetes assessed by $HbA_{1c}$ 5·7–6·4% without impaired fasting glucose was similar to that assessed by fasting glucose alone. Our results suggest that introduction of the new $HbA_{1c}$ criterion in addition to assessment of fasting plasma glucose could efficiently target patients who are most likely to progress to diabetes and allow for early intervention (panel).

A fifth of prediabetic individuals discordantly met the $HbA_{1c}$ but not the impaired fasting glucose criterion for diagnosis in our study, which is in line with results of the National Health and Nutrition Examination Survey (NHANES) in US adults, which showed a rate of 17·2%.[2] Conversely, with respect to screening accuracy, the NHANES had a sensitivity of 27% and specificity of 93%, and showed that 61% of individuals with prediabetes diagnosed by $HbA_{1c}$ also had impaired fasting glucose. Our results in a Japanese population showed lower sensitivity (21%) and specificity (91%), and only 50% of those with prediabetes diagnosed by $HbA_{1c}$ also had impaired fasting glucose. Evidence has suggested that screening performance using $HbA_{1c}$ values might differ according to ethnic origin.[4,5,15,16] Since only half of the prediabetic individuals in our study who met the new $HbA_{1c}$ criterion also had impaired fasting glucose, a discrepancy in the degree of overlap might be more likely in Japanese than in US adults. A recent report of the New Hoorn Study[17] indicated that correlations between glucose and $HbA_{1c}$ were moderate in the general population, although a strong correlation was seen in patients with known diabetes; therefore, the discrepancy in the degree of overlap might be higher for diagnosis of prediabetes than for diagnosis of type 2 diabetes. Other results of cross-sectional studies in US populations and Asian Indians[2–4,6] also reported a limited performance of the new $HbA_{1c}$ criterion for identification of individuals at increased risk of diabetes compared with screening by impaired fasting glucose or impaired glucose tolerance, although none of these studies prospectively investigated the subsequent risk of progression to diabetes.

In our study, diagnosis of prediabetes on the basis of both criteria was strongly predictive of the risk of future diabetes. The increased HR shown by the overlap between the two prediabetic criteria might suggest that the predictive power achieved through use of the two criteria was multiplied rather than having an additive effect. Additionally, this association was noted irrespective of the diagnostic criteria for incident diabetes. Two cohort studies offered prospective data for new criteria for diagnosis of prediabetes including $HbA_{1c}$ testing and the subsequent risk of diabetes.[7,8] The Atherosclerosis Risk in Communities (ARIC) study, which investigated the 10-year risk of diagnosed diabetes, reported that the 10-year cumulative incidence of diabetes was 10% for FPG lower than 5·6 mmol/L and $HbA_{1c}$ 5·7–6·5%, 7% for FPG 5·6–7·0 mmol/L and $HbA_{1c}$ less than 5·7%, and 23% for FPG 5·6–7·0 mmol/L and $HbA_{1c}$ 5·7–6·5%, suggesting a dual role for $HbA_{1c}$ and glucose in prediction of diabetes.[8] In Cederberg and colleagues' study,[7] which followed up 553 Finnish adults, 66% of incident cases of diabetes at 10 years were predicted by either $HbA_{1c}$ 5·7–6·4%, impaired fasting glucose, or impaired glucose tolerance, and a raised $HbA_{1c}$ 5·7–6·4% preceded diabetes in 33% of incident cases. Results of our study with a shorter follow-up showed that 86% of incident cases were predicted by either glucose tolerance or $HbA_{1c}$ 5·7–6·4%, and that in 54% of incident cases a range of $HbA_{1c}$ of 5·7–6·4% was seen at the baseline examination.

Two meta-analyses showed that the risk of development of diabetes established by $HbA_{1c}$ was similar to that described for FPG and 2-h glucose.[12,13] Gerstein and colleagues[12] reported that dysglycaemic individuals were at about a five-to-ten times increased risk of diabetes compared with individuals without impaired fasting

glucose or impaired glucose tolerance. In a systematic review,[13] raised $HbA_{1c}$ in the 5·0–6·5% range steeply increased the risk of diabetes and $HbA_{1c}$ 5·5–6·5% was associated with a substantially increased risk of future diabetes. By contrast with FPG, which reflects acute dysglycaemia, $HbA_{1c}$ reflects chronic hyperglycaemia, including postprandial glucose spikes.[1] The pathological disturbances of hepatic insulin resistance and reduced insulin secretion (first-phase and early-phase) led to isolated impaired fasting glucose.[18] In isolated impaired glucose tolerance, a severe deficit in late insulin secretion with muscle and hepatic insulin resistance leads to extended hyperglycaemia after a carbohydrate load.[18] Therefore, overlap with criteria for $HbA_{1c}$ and impaired fasting glucose might allow for assessment of a substantially increased risk of diabetes.

Although we cannot establish the underlying mechanism in this observational study, we noted that prediabetic individuals discordantly diagnosed by either impaired fasting glucose or $HbA_{1c}$ alone had significantly different cardiovascular risk profiles at the baseline diagnosis of prediabetes. The prevalence of obesity (BMI ≥25·0 kg/m²) was lower in individuals with prediabetes diagnosed by $HbA_{1c}$ alone compared with those diagnosed by impaired fasting glucose alone in this study. These different factors[14] might affect progression to diabetes within each case of discordantly diagnosed prediabetes. However, the results were fundamentally the same after adjustments in multiple regression models. Data from an epidemiological study on the insulin resistance syndrome showed that $HbA_{1c}$ predicted diabetes only in individuals with impaired fasting glucose.[19] On the other hand, the ARIC study reported that $HbA_{1c}$ values were associated with a risk of diabetes irrespective of baseline FPG.[8,20] In this study, even without impaired fasting glucose, the new $HbA_{1c}$ 5·7–6·4% criterion could be predictive of progression to diabetes, which was previously missed by screening for impaired fasting glucose.

In a more recent British prospective cohort study,[21] only 36% of incident cases of diabetes (defined as self-reported or $HbA_{1c}$ ≥6·5%, or both) arose from the 6% of the total study population with baseline $HbA_{1c}$ 6·0–6·4%, which suggests that most incident cases of diabetes occurred in those with baseline $HbA_{1c}$ lower than 6·0%. Although we used a different threshold for $HbA_{1c}$, 46% of incident cases were without raised $HbA_{1c}$ at baseline. Efficacy of the new $HbA_{1c}$ 5·7–6·4% criterion will improve as a screening test and will be more predictive when used with impaired fasting glucose criterion for identification of individuals at substantially increased risk of developing diabetes. Nonetheless, the prediabetic state only indicates an individual's glycaemic condition at a single point in time of the natural history of development of diabetes. An analysis from the Whitehall II study[22] showed that individuals who developed diabetes had raised FPG as early as 13 years before diagnosis of diabetes compared with those who did not develop diabetes. Further studies will be needed to investigate the long-term trajectories of clinical markers, including $HbA_{1c}$, before the diagnosis of diabetes, especially in non-western populations.

Although the $HbA_{1c}$ test has been standardised nationwide in Japan, there might be concerns about its cost and lack of standardisation in some countries. Investigations into how the predictive power would be improved by inclusion of simple risk factors for diabetes such as family history, obesity, or smoking habits and the derivation of algorithms would be of great importance. Also, whether introduction of $HbA_{1c}$ into glucose testing is appropriate for detection of not only future diabetes but also cardiovascular disease events and mortality should be studied in various ethnic groups.

Strengths of our study include the assessment of a large sample size with annual data for $HbA_{1c}$ and FPG and the investigation of a major topic in relation to the Asian population, in view of the increasing prevalence of prediabetes and diabetes.[23,24] Our findings through introduction of $HbA_{1c}$ criteria in addition to impaired fasting glucose for screening of prediabetic individuals

*Panel:* Research in context

**Systematic review**

We searched PubMed for studies published in English from March 1, 1996, to Dec 31, 2010, that assessed the effect of introduction of the new glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) 5·7–6·4% criterion into screening of prediabetes and those that assessed the risk of future diabetes according to a baseline diagnosis by raised $HbA_{1c}$, impaired fasting glucose concentrations, or impaired glucose tolerance. Search terms used were "glycated hemoglobin", "$HbA_{1c}$", "$A_{1c}$", "impaired fasting glucose", "impaired glucose tolerance", "glucose intolerance", "prediabetes", or "pre-diabetes". A meta-analysis[12] reported that dysglycaemic individuals were at a roughly five-to-ten times increased risk of diabetes compared with individuals without impaired fasting glucose or impaired glucose tolerance. A recent systematic review[13] reported that $HbA_{1c}$ 5·5–6·5% was associated with a substantially increased risk of future diabetes. Recent cross-sectional studies[2-5] reported that use of the $HbA_{1c}$ 5·7–6·4% criterion for screening reclassified a large number of individuals previously diagnosed as having prediabetes on the basis of impaired fasting glucose, and that $HbA_{1c}$ alone might miss prediabetes in many individuals. Two longitudinal studies[7,8] compared the risk of progression to diabetes according to a baseline diagnosis of prediabetes by the new $HbA_{1c}$ 5·7–6·4% criterion and the impaired fasting glucose criterion.

**Interpretation**

Our study provides data for a cross-sectional comparison of the new $HbA_{1c}$ criterion for prediabetes and impaired fasting glucose as predictors for progression to diabetes. We found that diagnosis of prediabetes by both the $HbA_{1c}$ criterion and impaired fasting glucose identified individuals at a substantially increased risk for progression to diabetes more effectively than the use of only one of these indicators. Even though the new $HbA_{1c}$ criterion identified fewer individuals at high risk than did impaired fasting glucose, the predictive value for progression to diabetes assessed by $HbA_{1c}$ 5·7–6·4% without impaired fasting glucose was similar to that assessed by fasting glucose alone. Previously, there has been little clarification of the characteristics of people who progress to diabetes in a large population study,[14] especially related to the performance of screening with the proposed new $HbA_{1c}$ criterion. Our results could contribute to targeting of people most likely to progress to diabetes and efficiently allow for early intervention.

contributed to identification of different groups of people who subsequently progressed to diabetes who would otherwise have been missed. These results have the potential to reduce the incidence of diabetes in the future by allowing such individuals to undertake strategies to prevent progression to diabetes. Our study also includes a systematic assessment of the incidence of diabetes with either FPG or $HbA_{1c}$ alone and both FPG and $HbA_{1c}$ diagnostic criteria for diabetes. Results suggested that use of both criteria could detect many individuals in need of early clinical care, in line with a recent study showing that use of either $HbA_{1c}$ or FPG alone identified only 63% of incident cases of diabetes defined by a combination of FPG and $HbA_{1c}$ criteria.[25]

Several limitations should be considered. First, data for the oral glucose tolerance test were not available for our study, and whether these data could have changed our results should be considered. Since we might have included individuals with postprandial hyperglycaemia in the category of $HbA_{1c}$ 5·7–6·4% alone, the risk of development of diabetes for this group of patients might be overestimated by comparison with investigations using data for oral glucose tolerance. Second, we cannot deny the possibility of selection bias due to study participants being those who underwent routine medical checkups, and thus who paid more attention to health issues than those who did not. All participants might not have been properly fasting, although the prevalence of diabetes, obesity, and smoking were similar to those in general population-based studies in Japan.[26] Since we assessed the development of diabetes yearly, the incidence might be overestimated, although we noted that the incident rate of diabetes was similar to that of general Japanese populations.[27,28] We also need to consider that there could be many confounding factors such as differences in dietary habit of the participants for which we were not able to fully adjust. Additionally, the effect of factors that might change $HbA_{1c}$ levels independently of glycaemia, such as anaemia or haemoglobinopathies, should be considered. Although the prevalence of haemoglobinopathies is reported to be very low in Japan (0·04%),[29] concern should be noted in some areas of southeast Asia that have high rates of haemoglobinopathies.[30]

In conclusion, diagnosis of prediabetes by introduction of the new $HbA_{1c}$ criterion in addition to assessment of impaired fasting glucose could identify prediabetic individuals with a substantially increased risk of progression to diabetes. Although the new $HbA_{1c}$ criterion identified fewer individuals at high risk than did impaired fasting glucose, the predictive value for progression to diabetes assessed by the $HbA_{1c}$ criterion alone was similar to that assessed by impaired fasting glucose alone. The two tests used together could target individuals most likely to progress to diabetes and allow for early intervention.

**Contributors**

YH contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, statistical analysis, and study supervision. SH, YA, SDH, HT, and YM contributed to the study concept and design, acquisition of data, drafting and critical revision of the manuscript, and technical or material support. KS, KF, and SK contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, and statistical analysis. HSh contributed to study concept and design and critical revision of the manuscript. NY contributed to study concept and design, acquisition of data, and critical revision of the manuscript. KK contributed to the study concept and design and acquisition of data. HSo contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, statistical analysis, funding, and study supervision. All authors were involved in the writing of the manuscript and approved the final version of this article.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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