of absolute risks since it is likely that each engine was developed independently, and a correlation between incidences of vascular complications is not accounted for in the development process.

Data from the 1,748 patients with type 2 diabetes in the Japan Diabetes Complications Study (JDCS) (26) and the Japanese Elderly Diabetes Intervention Trial (J-EDIT) (27) provide an opportunity to develop a comprehensive risk engine for Asian patients with type 2 diabetes. The aim of the current study was therefore to develop and validate an algorithm that separately calculates each risk of the first occurrence for five events: fatal and nonfatal CHD, fatal and nonfatal stroke, noncardiovascular mortality, overt nephropathy, and progression of retinopathy. This was done by fitting a multistate Cox regression model (28), an extension of the Cox model to multiple time-to-event end points, to the pooled data from these trials.

RESEARCH DESIGN AND METHODS

Patients and measurements

Design of the JDCS and the J-EDIT has been described in detail elsewhere (26,27). In the JDCS, 2,033 Japanese type 2 diabetes patients 40–70 years of age whose HbA$_{1c}$ levels were $\geq 7.0\%$ were randomized to a conventional treatment group and a lifestyle intervention group; throughout the paper, we present the National Glycohemoglobin Standardization Program value of HbA$_{1c}$ calculated as follows: 0.25 + 1.02 × JDC value (29). The latter group received education on lifestyle modification by telephone counseling and at each outpatient clinic visit in addition to usual care. The J-EDIT is a randomized, controlled trial of intensive and conventional treatments for diabetes that registered a total of 1,173 Japanese type 2 diabetes patients 65–85 years of age whose HbA$_{1c}$ levels were $\geq 8.1\%$, or $\geq 7.5\%$ with at least one of the following criteria: BMI ≥ 25 kg/m^2; blood pressure $\geq 130/85$ mmHg; serum total cholesterol ≥ 200 mg/dL (5.17 mmol/L) or LDL cholesterol ≥ 120 mg/dL (3.10 mmol/L) in participants without CHD; serum total cholesterol ≥ 180 mg/dL (4.65 mmol/L) or LDL cholesterol ≥ 100 mg/dL (2.59 mmol/L) in participants with CHD; triglycerides ≥ 150 mg/dL (1.68 mmol/L); and HDL cholesterol <40 mg/dL (1.03 mmol/L). The protocols of the JDCS and J-EDIT received approval from the ethical committees of all of the

participating institutes, and written informed consent was obtained from all patients before enrollment. The present analysis excluded patients who had any history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolemia (diagnosed clinically by markedly elevated LDL cholesterol levels with enlarged Achilles tendons and/or family history of premature coronary artery disease), type III hyperlipidemia (diagnosed by broad β-band on electrophoresis), nephrotic syndrome, serum creatinine levels >1.3 mg/dL (120 μmol/L), mean values of two spot urine examinations for an albumin excretion rate of 150 mg/g creatinine (17.0 mg/mmol) or more, microscopic hematuria, or other clinical findings indicating other renal diseases, preproliferative and proliferative retinopathy, and major ocular disease (e.g., glaucoma, dense cataract, or history of cataract surgery). Baseline data were collected for demographics, results of clinical examinations, laboratory measurements performed at local laboratories, and lifestyle factors such as dietary content and smoking status determined by self-reported questionnaires. Leisure-time physical activity (LTPA) was also assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study (30). The patients were asked to report their average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golfing, tennis, swimming, aerobics dancing, cycling, and other miscellaneous exercise as specified by each patient. The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in metabolic equivalents (METs), and overall activities were summed to yield a MET/h score per week (31). Data management was conducted by a central data center. Follow-up data were collected through a standardized annual report from each investigator. Non-HDL cholesterol (NHDL-C) levels were calculated by total cholesterol subtracted by HDL cholesterol. LDL cholesterol levels were calculated using the Friedewald formula, that is, NHDL-C subtracted by triglycerides divided by 5 if triglyceride levels are <400 mg/dL (4.48 mmol/L); otherwise, LDL cholesterol levels were treated as missing data.

End points

End points were five time-to-event variables: fatal or nonfatal CHD, fatal

or nonfatal stroke, noncardiovascular mortality, overt nephropathy defined by persistent proteinuria, and progression of retinopathy since randomization. The definitions of the events have been described in detail elsewhere (12,13,27,32). In brief, diabetic retinopathy was determined annually by qualified ophthalmologists at each institute using the international diabetic retinopathy and diabetic macular edema disease scales (33) with minor modification: stage 0, no retinopathy; stage 1, hemorrhage and hard exudates; stage 2, soft exudates; stage 3, intraretinal microvascular abnormalities and venous changes, including beading, loop, and duplication; and stage 4, new vessels, vitreous hemorrhage, fibrous proliferation, and retinal detachment. A retinopathy event was progression to stage 3 or 4. A nephropathy event was defined as the development of overt nephropathy (spot urinary albumin excretion >33.9 mg/mmol creatinine in two consecutive samples) (12). Macrovascular events included the occurrence of fatal and nonfatal definite CHD (angina pectoris or myocardial infarction) and fatal and nonfatal stroke. The diagnosis of angina pectoris and myocardial infarction was according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease project, and diagnosis of stroke was according to guidelines defined by the Ministry of Health, Labour, and Welfare of Japan (32). Adjudication of end points was performed by central committees comprised of experts in each complication based on additional data such as those obtained by computed tomography or magnetic resonance imaging of the brain or sequential changes in electrocardiograms.

Statistical analysis

The JDCS/J-EDIT (JJ) risk engine calculates each risk of the first occurrence within a user-specified time point for the five events described above. The occurrences of these events are viewed as transitions between disease states and were modeled by a multistate model that follows the Markov renewal process (28). The disease states and transitions assumed in the multistate model are detailed in Supplementary Data. We fit a multistate model using a standard procedure for the stratified Cox regression model. That is, we assumed that baseline intensities for any of the transitions were possibly different but that transition intensities to a disease state share common

hazard ratios (HRs) for risk factors. The following risk factors were screened through a backward variable selection with the critical value of $P = 0.1$: age, sex, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure (SBP), NHDL-C, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, log-transformed urine albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate, atrial fibrillation, smoking status, alcohol intake, and LTPA. BMI was categorized by cutoff points of 18.5 and 25 kg/m^2. LTPA was categorized by the cutoff point of 3.8 METs-h/week, which corresponds to the intensity of home activity or conditioning exercise (31). HRs in this model were estimated by maximizing the partial likelihood, and then baseline intensity functions were calculated by the Breslow estimator. Missing data were substituted using the multiple imputation method.

We assessed the predictive accuracy of the 5-year risks based on the JJ risk engine using 10-fold cross-validation, i.e., we performed 10 rounds of cross-validation using different partitions. One round of cross-validation involved randomly partitioning a sample of data on 1,748 patients into complementary subsets, fitting the stratified Cox regression model to one subset of 90% of patients, and validating the model on the remaining subset with the criteria described below. We compared hazards for end points between tertiles of the calculated 5-year risks from the 10-fold cross-validation by the Cox regression. Calibration, namely, how closely the prediction reflected observed events, was assessed for each event by the Hosmer-Lemeshow test and the mean of observed-to-predicted (O/P) ratios, which was calculated as the mean of ratios of the observed-to-expected events across the strata used in the Hosmer-Lemeshow test. Discrimination, the ability to distinguish between those who experienced the event and those who did not, was evaluated using Harrell C statistics, the proportion of all patient pairs in which the predictions of the model and observed events were concordant. Further, we constructed a reclassification table of macro- and microvascular complications (34).

All analyses were conducted by the central data center with the use of SAS software version 9.2 (SAS Institute, Cary, NC). The authors had full access to the data and take responsibility for their integrity. All reported P values for statistical tests are two tailed, and $P < 0.05$ was taken to indicate statistical significance.

RESULTS—The mean ± SD (range) age and HbA_{1c} level at baseline of the 1,748 Japanese type 2 diabetic patients was 62.1 ± 8.6 (40–84) years and 7.9 ± 1.2 (6.0–15.8)%, respectively, and 49.9% of the subjects were women. Their mean baseline values indicated that the subjects had good control of weight (BMI = 23.2 ± 3.1 kg/m^2; waist circumference = 80.3 ± 9.6 cm), blood pressure (SBP = 132.9 ± 16.0 mmHg), and serum cholesterol levels (NHDL-C = 3.78 ± 0.90 mmol/L; LDL cholesterol = 3.16 ± 0.82 mmol/L; HDL cholesterol = 1.43 ± 0.44 mmol/L; triglycerides = 1.39 ± 0.88 mmol/L). Their baseline ACR levels were quite low, with a median ± IQR of 1.8 ± 3.0 mg/mmol, as we excluded those with ACR of 17.0 g/mmol or more. Current smokers and past smokers accounted for 24.4 and 24.0%, respectively, of patients. The median (IQR) LTPA at baseline was 10.5 (1.6–22.5) METs-h/week, and 34.0% of patients had no exercise habit (<3.8 METs-h/week). During the median follow-up of 7.2 years, among the 1,748 subjects, we observed 96 (5.5%) events of fatal or nonfatal CHD, 89 (5.1%) fatal or nonfatal strokes, 71 (4.1%) overt nephropathies defined by persistent proteinuria, and 64 (3.7%) noncardiovascular deaths. Of the 1,297 patients without retinopathy at baseline, 415 (32.0%) developed retinopathy. Of the 866 patients who had retinopathy or developed retinopathy after baseline, 113 (13.0%) had progression to retinopathy of stage 3 or 4.

The backward variable selection procedure identified 11 baseline risk factors

Table 1—*HRs of risk factors incorporated in the best-fitting multistate Cox regression model*

	CHD			Stroke			Noncardiovascular mortality		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sex (woman/man)	0.41	0.24 0.70	<0.01	0.46	0.29 0.73	<0.01	0.55	0.29 1.04	0.07
Age (+10 years)	1.38	1.02 1.85	0.04	1.55	1.17 2.06	<0.01	2.44	1.70 3.50	<0.01
HbA_{1c} (+1%)	1.22	1.02 1.45	0.03	1.23	1.04 1.44	0.02			
BMI (<18.5/18.5–25 kg/m^2)							3.22	1.40 7.37	0.01
BMI (≥ 25/18.5–25 kg/m^2)							1.16	0.60 2.21	0.66
SBP (+10 mmHg)	1.13	0.98 1.31	0.10	1.16	1.00 1.33	0.045			
NHDL-C (+1 mmol/L)	1.56	1.26 1.93	<0.01	1.38	1.10 1.74	0.01			
Atrial fibrillation (yes/no)				12.48	3.77 41.29	<0.01			
Current smoker (yes/no)	1.67	1.00 2.81	0.052				2.11	1.04 4.26	0.04
LTPA (≥3.8/<3.8 METs-h/week)				0.63	0.39 1.01	0.053	0.57	0.33 1.01	0.054

	Overt nephropathy			Retinopathy		
Age (+10 years)				1.16	1.04 1.30	0.01
HbA_{1c} (+1%)	1.28	1.08 1.53	0.01	1.32	1.25 1.40	<0.01
Years after diagnosis (+1 years)				1.04	1.03 1.06	<0.01
BMI (<18.5/18.5–25 kg/m^2)				0.67	0.43 1.03	0.07
BMI (≥25/18.5–25 kg/m^2)				1.22	0.99 1.49	0.06
SBP (+10 mmHg)	1.14	0.97 1.33	0.11			
Log ACR (+1 unit)	3.02	2.16 4.23	<0.01	1.11	1.01 1.22	0.03
Atrial fibrillation (yes/no)	5.54	0.74 41.49	0.10			
Current smoker (yes/no)	2.18	1.28 3.71	<0.01			

for macro- and microvascular complications and noncardiovascular mortality. Table 1 shows the HRs, 95% CIs, and P values for these risk factors. Significant modifiable risk factors were HbA_{1c} and NHDL-C for CHD, HbA_{1c}, SBP, and NHDL-C for stroke, BMI <18.5 kg/m² and being a current smoker for noncardiovascular mortality, HbA_{1c} and being a current smoker for overt nephropathy, and HbA_{1c} for retinopathy. Having an exercise habit was associated with reduced risks of stroke and mortality, although with only borderline statistical significance. All of the risk factors that were retained through the variable selection procedure were incorporated into the JJ risk engine. The algorithm of the JJ risk engine is described in Supplementary Data.

The performance of the JJ risk engine was evaluated by several validation criteria. Tertile Cox regression showed that the 5-year risks calculated by the JJ risk engine effectively classified populations at low and high risk for each complication. The HRs (95% CI) of the second and third tertiles compared with the first tertile were 2.09 (1.07–4.09) and 5.22 (2.84–9.58) for CHD; 1.78 (0.96–3.30) and 3.32 (1.86–5.92) for stroke; 2.14 (1.09–4.18) and 3.17 (1.65–6.09) for noncardiovascular mortality; 1.54 (0.55–4.34) and 10.59 (4.56–24.59) for overt nephropathy; and 1.18 (0.58–2.40) and 2.56 (1.37–4.81) for progression of retinopathy.

Table 2 shows the predictive accuracy of the JJ risk engine regarding calibration and discrimination. The O/P ratios for each complication, including noncardiovascular mortality, ranged between 0.93 and 1.08, and Hosmer-Lemeshow tests did not show any significant deviations between the observed and predicted events. In contrast, the UKPDS risk engine (5,6) overestimated CHD risk in Japanese patients (O/P ratios [Hosmer-Lemeshow P]: 0.30 [P < 0.01] for CHD and 0.72 [P = 0.54] for stroke) (Table 2). Discrimination according to C statistics was high for CHD, noncardiovascular mortality, and overt nephropathy (0.696–0.767) but was moderate for stroke and progression of retinopathy (0.636 and 0.614).

Table 3 compares risk classification by the 5-year risk of macrovascular disease based on the JJ risk engine with that based on the UKPDS risk engine. By the UKPDS risk engine, more than half of patients had a macrovascular risk of 10% or more (249 of the 376 cases and 697

of the 1,372 noncases), as expected by the tendency of overestimation The sensitivity and specificity of the UKPDS risk engine with a cutoff value of 10% risk were 66.2 and 49.2%, respectively. In contrast, only 101 of the 376 cases (26.9%) who developed any of the events had a macrovascular risk of 10% or more based on the JJ risk engine, yielding sensitivity of 26.9% and specificity of 89.1%.

Table 4 shows how the combination of 5-year risks of macro- and microvascular complications based on the JJ risk engine classified low-risk and high-risk patients. If we combined macro- and microvascular risks, 73 of 376 cases (19.4%) and 187 of 1,372 noncases (13.6%) were newly classified as a high-risk population, and sensitivity increased up to 46.3% while specificity was maintained at 75.4%. The net reclassification

improvement (total of sensitivity and specificity in this case) was improved by 5.7% (P = 0.02).

To illustrate the use of the JJ risk engine, consider two Japanese men 60 years of age with simple diabetic retinopathy and without atrial fibrillation who do not have smoking and exercise habits. The clinical characteristics of both patients are HbA_{1c} = 9%, duration of diabetes = 20 years, BMI = 23 kg/m², NHDL-C = 3.88 mmol/L, and ACR = 6.79 mg/mmol creatinine. The SBP of one patient is 120 mmHg. His leading risk is estimated to be the progression of retinopathy (5-year risk, 15.5%), and his macrovascular risks are moderate (9.2% for CHD and 9.6% for stroke). His 5-year risks of noncardiovascular death and overt nephropathy are low (4.8 and 3.7%, respectively). The other patient has

Table 2—*Predictive accuracy of the JJ risk engine in 1,748 patients*

	Calibration				Discrimination	
	Mean predicted 5-year risk	Observed 5-year risk	O/P ratio	P†	C statistic	95% CI
CHD	2.70%	2.92%	1.08	0.14	0.725	0.656–0.793
By the UKPDS risk engine	(9.66%)	—	(0.30)	(<0.01)	(0.695)	(0.626–0.764)
Stroke	3.36%	3.26%	0.97	0.12	0.636	0.564–0.708
By the UKPDS risk engine	(4.52%)	—	(0.72)	(0.54)	(0.638)	(0.566–0.711)
Noncardiovascular mortality	2.08%	2.12%	1.02	0.12	0.696	0.613–0.778
Overt nephropathy	2.28%	2.40%	1.04	0.11	0.767	0.690–0.845
Progression of retinopathy*	10.96%	10.20%	0.93	0.13	0.614	0.524–0.705

*Patients without diabetes retinopathy at baseline were excluded. †The Hosmer-Lemeshow test with eight degrees of freedom. P < 0.05 indicates significant deviation between predicted and observed events.

Table 3—*Risk classification of the 1,748 patients according to 5-year risks of macrovascular disease based on the JJ risk engine and the UKPDS risk engine*

	5-Year risk by the JJ risk engine*						
5-Year risk by the UKPDS risk engine*	<5%		5–10%		10% or more		Total
Patients who developed events							
<5%	37	9.8%	2	0.5%	0	0.0%	39
5–10%	66	17.6%	19	5.1%	3	0.8%	88
10% or more	37	9.8%	114	30.3%	98	26.1%	249
Total	140		135		101		376
Patients who did not develop any events							
<5%	245	17.9%	7	0.5%	0	0.0%	252
5–10%	341	24.9%	78	5.7%	4	0.3%	423
10% or more	202	14.7%	349	25.4%	146	10.6%	697
Total	788		434		150		1,372

*Data are n and percent. Probability of any occurrence of CHD or stroke within 5 years.

Table 4—*Risk classification of the 1,748 patients according to 5-year risks of macro- and microvascular diseases based on the JJ risk engine*

5-Year risk of microvascular disease†	5-Year risk of macrovascular disease*							
	<5%		5–10%		10% or more		Total	
Patients who developed events								
<5%	79	21.0%	48	12.8%	19	5.1%	146	
5–10%	40	10.6%	35	9.3%	20	5.3%	95	
10% or more	21	5.6%	52	13.8%	62	16.5%	135	
Total	140		135		101		376	
Patients who did not develop any events								
<5%	601	43.8%	215	15.7%	40	2.9%	865	
5–10%	115	8.4%	104	7.6%	34	2.5%	240	
10% or more	72	5.2%	115	8.4%	76	5.5%	267	
Total	759		434		150		1,372	

*Data are n and percent. Probability of any occurrence of CHD or stroke within 5 years. †Probability of any occurrence of overt nephropathy defined by persistent proteinuria or progression of retinopathy within 5 years.

an SBP of 180 mmHg. His leading risks are macrovascular diseases (16.1% for CHD and 17.6% for stroke), and his microvascular risks are moderate (7.8% for nephropathy and 13.6% for retinopathy). The risk of noncardiovascular mortality is estimated to be 4.0%.

CONCLUSIONS—In this study, we developed a novel risk engine that integrates modifiable lifestyle and clinical risk factors, including HbA_{1c}, BMI, SBP, NHDL-C, current smoking, and LTPA into the risks of a first occurrence of macro- and microvascular complications. We confirmed that the risk engine performed reasonably well and that combining macro- and microvascular risks improved the classification of low-risk and high-risk patients by a net reclassification improvement of 5.7%. In contrast, the UKPDS risk engine overestimated CHD risk, and this tendency is consistent with a previous report in Asian patients (18). A web application for the JJ risk engine, which works in both Windows and Macintosh environments, is available at http://www.biostatistics.jp/prediction/jjre.

With the advent of modern therapeutics, especially hypoglycemic and antihypertensive agents, the early identification of high-risk patients is an appealing strategy (35). A novelty of the JJ risk engine is that it allows risk classification based on the risk not only of CVD but also of renal and eye diseases. Although the prevalence of micro- or macroalbuminuria in Asian hypertensive diabetes is alarmingly high (36), most of the progression to overt nephropathy occurs in a small fraction of patients with elevated HbA_{1c} and SBP values

and a smoking habit (12). In this study, patients in the fourth quartile of the calculated risk developed overt nephropathy at a rate 10 times greater than those in the first quartile. Most risk engines are specific to CVD; however, greater emphasis on the risk of microvascular diseases should be placed when assessing risk among diabetic patients given that diabetic nephropathy and retinopathy are major causes of ESRD and blindness, respectively. Combining macro- and microvascular risks resulted in the net reclassification improvement of 5.7% (P = 0.02) and a sensitivity and specificity of 46.3 and 75.4%, respectively; only 16.5% of cases were classified as the high-risk population for macro- and microvascular diseases and only 43.8% of noncases were in the low-risk population (Table 4). Thus, the discriminatory power of the JJ risk engine was only moderate, despite the statistically significant improvement in prediction, and exploring novel risk factors would be of particular importance for more accurate risk classification.

The JJ risk engine shares features similar to those with previously developed risk engines. The predictors of CHD are the same as in the UKPDS risk engine (5) except for the inclusion of NHDL-C instead of the total cholesterol–to–HDL cholesterol ratio. Donnan et al. (7) added diabetes duration, treated hypertension, height, and two interaction terms into their model, and the risk equation of the HKDR includes diabetes duration, estimated glomerular filtration rate, and ACR additionally but does not use HbA_{1c} (18). A recent cohort study in Japan also

suggested that the progression of the albuminuria stage is a risk factor of CVD (37). In contrast, log ACR was not associated with CHD or stroke in our study. This discordant observation would be attributable to the exclusion of low microalbuminuria in our study. The elevation of ACR within a range of normoalbuminuria may not lead to an increase in the risk of CVD. We also found that the UKPDS risk engine overestimated CHD risk (Table 2) and the C statistic of the JJ risk engine (0.725) was slightly higher than that of the risk equation of the HKDR (0.704) (18), indicating that the JJ risk engine may outperform the previously developed risk engines for the prediction of CHD. For the prediction of stroke, we did not identify smoking status and years after diagnosis as predictors, which are included in the UKPDS risk engine (6). The risk equation from the Swedish National Diabetes Register incorporates the use of antihypertensive drugs and lipid-lowering drugs as predictors (9). However, medical therapies are not considered in the current analysis, since the effects of medications on vascular complications were likely to be confounded by other clinical factors. In contrast to CHD, the C statistic of the JJ risk engine (0.636) was similar to the UKPDS risk engine (0.638) and lower than the risk equation of the HKDR (0.749) (17). With regard to lifestyle factors, we identified LTPA as a risk factor for stroke and noncardiovascular mortality, although the statistical significance was borderline. On the other hand, BMI, which has been recognized as one of the most important risk factors in the deterioration of type 2 diabetes, was not associated with CVD. We previously reported that the BMI of Japanese patients is much lower than that of white patients, although in those reports, other patient characteristics were similar in terms of age, HbA_{1c}, and daily energy intake (10,11). Our findings run contrary to the results of studies of white patients, but data on diet in diabetic patients are sparse, particularly in Asia. In this study, the contribution of lifestyle factors to the risk assessment appears to be limited, and the associations between lifestyle and diabetes complications are worthy of further research.

One important feature of this study is that we analyzed pooled data from two nationwide clinical trials in Japan. The end points were defined similarly in both trials and follow-up was performed by diabetes specialists, ensuring data of relatively high quality. Patients generally

had fair or good glycemic, weight, blood pressure, and lipid control. The major difference between the two trials was eligible age, i.e., age between 40 and 70 years in the JDCS and age between 65 and 85 years in the J-EDIT. Prior to pooling the datasets, we compared important clinical factors between patients in the two trials and found no notable differences except for age; therefore, pooling of the datasets was considered to be valid. Consequently, the study population in the present analysis included subjects spanning several decades, i.e., those from 40 to 84 years. This can be expected to enhance the generalizability of the algorithm.

Statistical modeling can be much more complex if we handle multiple events simultaneously. To the best of our knowledge, this is the first study that applies a multistate model to the construction of a risk engine. It is notable that these events are not inherently independent and the JJ risk engine calculates each probability of the first occurrence for five events. Thus, if the risk of an event (e.g., overt nephropathy) was increased by a risk factor (e.g., log ACR), the probability of the first occurrence of other events (e.g., stroke) can decrease theoretically even if there are no direct associations with the risk factor.

Several limitations warrant mention. First, transportability of prognostic information is critical, but in this study we evaluated only the internal validity. Thus, external validation is required in other populations. Second, updating the algorithm by long-term follow-up data or pooled analysis with other studies in Asia is desirable given that the size of our cohort is relatively small and the observed events of CVD and overt nephropathy in this population were relatively few. Third, we included angina pectoris and transient ischemic attack as components of the cardiovascular events, although they are soft end points. Consequently, the JJ risk engine would provide macrovascular risks higher than those by other risk engines based on only hard cardiovascular events. Fourth, data on peripheral arterial disease and hemoglobin levels were not available. These factors were included as inputs into the HKDR all-cause mortality risk score (19), and peripheral arterial disease is a clinically relevant cardiovascular outcome. Fifth, the use of aspirin, which might increase the risk of hemorrhagic stroke, was not investigated. Finally, we defined overt nephropathy as the presence of persistent proteinuria, since an elevated

urinary albumin excretion due to nondiabetic renal lesions or conditions is not rare.

In conclusion, the risk engine allowed accurate and comprehensive risk assessment of macro- and microvascular complications, although external validation is required in other populations. The calculated absolute risks of vascular complications can be used in risk classification for individual patients, health economic simulations, and estimation of the burden of the disease.

References
1. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30: 1292–1293
2. Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJP. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia 2009;52: 2001–2014
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
4. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–2140
5. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679

6. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke 2002; 33:1776–1781
7. Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. Diabetes Care 2006;29:1231–1236
8. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyörälä K; DECODE Study Group; European Diabetes Epidemiology Group. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. Diabetologia 2004;47:2118–2128
9. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Nilsson PM, Gudbjörnsdottir S; Swedish National Diabetes Register. Risk prediction of cardiovascular disease in type 2 diabetes: a risk equation from the Swedish National Diabetes Register. Diabetes Care 2008;31:2038–2043
10. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. Lancet 2003; 361:85
11. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N; Japan Diabetes Complications Study Group. Energy intake and obesity in Japanese patients with type 2 diabetes. Lancet 2004;363:248–249
12. Katayama S, Moriya T, Tanaka S, et al.; Japan Diabetes Complications Study Group. Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:1025–1031
13. Kawasaki R, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS). Diabetologia 2011;54:2288–2294
14. Sone H, Mizuno S, Yamada N. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005;352:1925–1927; author reply 1925–1927
15. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO Multinational Study of Vascular Disease in Diabetes: general description and morbidity. Diabetologia 2001;44(Suppl. 2):S3–S13
16. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002;287:2519–2527
17. Yang X, So WY, Kong AP, et al. Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care 2007;30: 65–70

18. Yang X, So WY, Kong AP, et al. Development and validation of a total coronary heart disease risk score in type 2 diabetes mellitus. Am J Cardiol 2008;101:596–601

19. Yang X, So WY, Tong PC, et al.; Hong Kong Diabetes Registry. Development and validation of an all-cause mortality risk score in type 2 diabetes. Arch Intern Med 2008;168:451–457

20. Yang X, Ma RC, So WY, et al. Development and validation of a risk score for hospitalization for heart failure in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2008;7:9

21. Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005;28:799–805

22. Kokkinos P, Myers J, Nylen E, et al. Exercise capacity and all-cause mortality in African American and Caucasian men with type 2 diabetes. Diabetes Care 2009;32:623–628

23. Marwick TH, Hordern MD, Miller T, et al.; Council on Clinical Cardiology, American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Nutrition, Physical Activity, and Metabolism; Interdisciplinary Council on Quality of Care and Outcomes Research. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:3244–3262

24. Colberg SR, Sigal RJ, Fernhall B, et al.; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010;33:e147–e167

25. Müller-Riemenschneider F, Holmberg C, Rieckmann N, et al. Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. Arch Intern Med 2010;170:719–724

26. Sone H, Tanaka S, Iimuro S, et al.; Japan Diabetes Complications Study Group. Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes: a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). Diabetologia 2010;53:419–428

27. Araki A, Iimuro S, Sakurai T, et al.; Japanese Elderly Diabetes Intervention Trial Study Group. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial—study design, baseline characteristics and effects of intervention. Geriatr Gerontol Int 2012;12(Suppl. 1):7–17

28. Andersen PK, Keiding N. Multi-state models for event history analysis. Stat Methods Med Res 2002;11:91–115

29. The Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of hemoglobin A1c in Japan: from JDS to NGSP values [Internet]. Available from http://www.jds.or.jp/jds_or_jp0/uploads/photos/813.pdf. Accessed 31 January 2012

30. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003;107:2435–2439

31. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–1581

32. Sone H, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. 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). J Clin Endocrinol Metab 2011;96:3448–3456

33. Wilkinson CP, Ferris FL 3rd, Klein RE, et al.; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677–1682

34. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172; discussion 207–212

35. National Institute for Clinical Excellence. Inherited Clinical Guideline H. Management of type 2 diabetes: management of blood pressure and blood lipids. London: National Institute for Clinical Excellence [article online], 2002. Available from http://www.nice.org.uk/nicemedia/pdf/NICE_INHERITEd_Hv8.pdf. Accessed at 25 April 2011

36. Wu AY, Kong NC, de Leon FA, et al. An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) Study. Diabetologia 2005;48:17–26

37. Yokoyama H, Araki S, Haneda M, et al.; Japan Diabetes Clinical Data Management Study Group. Chronic kidney disease categories and renal-cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study (JDDM25). Diabetologia 2012;55:1911–1918

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes

COMMENTARY

Commentary on the United Kingdom Prospective Diabetes Study outcomes model 2: Need for long-term follow up and quality of life data in Asian patients

A paper by Hayes et al.[1] published in Diabetologia in June 2013 reports an updated version of the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model developed on the basis of data from 5,102 patients from the original UKPDS and 4,031 survivors enrolled in the 10-year post-trial study. Given the longevity of patients with diabetes, there is no doubt that accurate simulation of lifetime outcomes requires data with a minimum follow-up period of more than 10 years.

Considerable efforts have been devoted to developing models for simulating outcomes of patients with diabetes. Such models can be useful in two different situations: first, medical decision-making; for example, recommendation of statin therapy based on absolute cardiovascular risk; and second, health technology assessment based on efficacy and cost-effectiveness. In the UK, the standard of care recommended by the health technology assessment body – the National Institute for Health and Clinical Excellence (NICE) – are determined on the basis of the results of clinical trials and cost-effectiveness analysis. Sitagliptin is, for example, recommended by NICE Short Clinical Guideline 87 as an additional agent instead of a sulfonylurea in second-line therapy because of its incremental cost-effectiveness ratio of £1,567 per one quality-adjusted life year (QALY) as compared with rosiglitazone[2]. In that analysis, the QALY of diabetes

patients was estimated by computer simulation using the UKPDS outcomes model.

Table 1 summarizes previously developed health economic models for diabetes. A health economic model for diabetes generally consists of three elements: disease states and transitions; risk equations; and utility values of each disease state ranging from 0 to 1. The incidence of a diabetic complication is viewed as a transition from a 'no-complication' state to the disease state. The probabilities of each transition depend on the risk factors shown in Table 1, and the relationships between the probabilities and the risk factors are expressed as risk equations[1,3–6]. Simulation by the UKPDS outcomes model 2 is carried out as the following steps on an annual cycle. First, at time-point $t = 0$, risk factors and event history of patients are input into risk equations, yielding the probabilities of transition. Second, mortality is calculated at $t = 0$ by using a risk equation. Mortality depends on the first step; that is, it will be higher if a transition to a diabetic complication occurs at $t = 0$. Third, in the case of death, the calculation is terminated; otherwise, information on risk factors and event history is updated at $t = 1$, and the same calculation is repeated annually until death. A utility value, which is usually estimated by quality-of-life (QOL) questionnaires, reflects the quality of a patient's lifetime with the corresponding diabetic complication. The simulated lifetime is weighted by utility values to account for its quality, yielding an estimate of QALY. For more details, see supplementary materials in Hayes et al.[1]

Among the models in Table 1, the UKPDS outcomes model 2, the JJ risk engine[3] and the risk equations from the Swedish National Diabetes Register[4] were developed by using individual patient data, but the others were constructed by synthesizing summary statistics reported in the literature, such as incidence rate and mean QOL value[5,6]. The UKPDS followed more than 4,000 patients for the longest period, making it possible to simulate end-stage events, such as second myocardial infarction and stroke. Furthermore, QOL data are available only in the UKPDS[1]. Although their follow-up length was relatively long, the Japanese study observed few incidents of second cardiovascular events, blindness, end-stage renal disease or amputation as a result of their low incidence and the limited sample size[3]. In contrast, the Swedish National Diabetes Register is a registry of data from clinical practice, so although it has a large sample size, the incidence of diabetic complications has not been adjudicated by a central committee as is usually done in prospective studies[4].

As expected, cardiovascular risks vary across study populations: the incidence of myocardial infraction and stroke per 1,000 person-years were, respectively, 11.3 and 5.6 in the UK[1], and 13.5 and 12.1 in Sweden[4]. By contrast, those of coronary heart disease and stroke were 7.6 and 7.1, respectively, in the Japanese study[3]. Given the apparent lower risk of coronary heart disease in Japan, models developed in Caucasian populations should not be used for simulation of Asian patients. To illustrate this, consider a Japanese man aged 60 years without

*Corresponding author. Hirohito Sone
Tel.: +81-25-368-9024 Fax: +81-25-368-9024
E-mail address: sone@med.niigata-u.ac.jp

Table 1 | Summary of health economic models for diabetes

Study country	Data	Risk factors incorporated in risk equations	Disease states				QOL
			Cardiovascular	Eye	Renal	Other	
UKPDS[1] The UK	n = 5,102 30-year follow-up	Age, sex, duration of diabetes, ethnicity, smoker, SBP, HbA1c, LDL, HDL, BMI, eGFR, heart rate, atrial fibrillation, PVD, albuminuria, hemoglobin, white blood cells	MI, stroke, IHD, CHF	Blindness	Renal failure	Diabetic ulcer, amputation	Available
JDCS/J-EDIT[3] Japan	N = 1,748 8-year follow-up	Age, sex, duration of diabetes, current smoker, leisure-time physical activity, SBP, HbA1c, non-HDL cholesterol, BMI, albumin-to-creatinine ratio, atrial fibrillation	CHD, stroke	Progression of retinopathy	Overt nephropathy		No
SNDR[4] Sweden	N = 29,034 5-year follow-up	Age, sex, duration of diabetes, smoker, blood pressure, HbA1c, total-to-HDL cholesterol ratio, LDL, BMI, albuminuria, history of events before diagnosis	MI, heart failure, IHD, stroke				No
CDC[5] The USA	Literature-based	Age, sex, race or ethnicity, hypertension, hypercholesterolemia, current smoker	CHD, angina, cardiac arrest/myocardial infarction, stroke	Photocoagulation, blindness	Low- or high-macroalbuminuria, clinical nephropathy, ESRD	Peripheral nephropathy, lower extremity amputation	Available
CORE[6] Switzerland	Literature-based	Age, sex, duration of diabetes, race, smoker, blood pressure, HbA1c, lipid levels, BMI, baseline complications	MI, angina, CHF, stroke	Retinopathy, macular edema, cataract	Nephropathy	Neuropathy, PVD, foot amputation, hypoglycemia, ketoacidosis, lactic acidosis	Available

BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CHF, congestive heart failure; CORE, Center for Outcomes Research; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; IHD, ischemic heart disease; J-EDIT, Japanese Elderly Diabetes Intervention Trial; JDCS, Japan Diabetes Complications Study; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; PVD, peripheral vascular disease; QOL, quality of life; SBP, systolic blood pressure; SNDR, Swedish National Diabetes Register; UKPDS, United Kingdom Prospective Diabetes Study.

diabetic retinopathy and atrial fibrillation who does not have smoking or exercise habits. The clinical characteristics of the patient are glycated hemoglobin 9%, duration of diabetes 20 years, body mass index 23 kg/m^2, systolic blood pressure 180 mmHg, total cholesterol 210 mg/dL, high-density lipoprotein cholesterol 60 mg/dL and albumin-to-creatinine ratio 60 mg/g. His 5-year risk of coronary heart disease calculated by the JJ risk engine is 9.3%, whereas that calculated by the UKPDS risk engine is 15.5%, giving an approximately 1.7-fold overestimation.

Health technology assessment is an emerging political issue in Japan – as indicated by the interim report published by Japan's Central Social Insurance Medical Council (Chuikyo) on 6 November 2013, cost-effectiveness using QALY as a default outcome measure is expected to be introduced in Japan to determine health insurance coverage or the price of pharmaceuticals and medical devices. As aforementioned, extrapolating models for diabetes to a population of different ethnicity is risky. Thus, there is an urgent need for long-term follow up and QOL data among Asian patients.

Shiro Tanaka[1], Sachiko Tanaka[2], Hirohito Sone[3]*
[1]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, [2]EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, and [3]Department of Hematology, Endocrinology and Metabolism, Niigata University Faculty of Medicine, Niigata, Japan

REFERENCES

1. Hayes AJ, Leal J, Gray AM, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia 2013; 56: 1925–1933.
2. National Institute for Health and Clinical Excellence. NICE short clinical guideline 87. Type 2 diabetes: newer agents Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes, 2009. Available at http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf [Accessed 1 January 2013].
3. Tanaka S, Tanaka S, Iimuro S, et al. Predicting macro- and microvascular complications in type 2 diabetes: the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine. Diabetes Care 2013; 36: 1193–1199.
4. Ahmad Kiadaliri A, Gerdtham UG, Nilsson P, et al. Towards renewed health economic simulation of type 2 diabetes: risk equations for first and second cardiovascular events from Swedish register data. PLoS ONE 2013; 8: e62650.
5. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002; 287: 2542–2551.
6. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin 2004; 20(Suppl 1): S5–S26.

Effect of Postmenopausal Status and Age at Menopause on Type 2 Diabetes and Prediabetes in Japanese Individuals: Toranomon Hospital Health Management Center Study 17 (TOPICS 17)

YORIKO HEIANZA, RD, MSC[1,2,3]
YASUJI ARASE, MD, PHD[2,4]
SATORU KODAMA, MD, PHD[1,2]
SHIUN DONG HSIEH, MD, PHD[2,4]
HIROSHI TSUJI, MD, PHD[2,4]

KAZUMI SAITO, MD, PHD[1,2,5]
HITOSHI SHIMANO, MD, PHD[3]
SHIGEKO HARA, MD, PHD[2,4]
HIROHITO SONE, MD, PHD, FACP[1,2]

OBJECTIVE—Findings on the effect of menopause or age at menopause on the presence of hyperglycemia are controversial, and why women after menopause have a higher probability of having hyperglycemia than men in the same age range remains unknown.

RESEARCH DESIGN AND METHODS—We reviewed data on 29,189 men, 6,308 premenopausal women, and 4,570 postmenopausal women in Japan. Odds ratios (ORs) for diabetes or prediabetes indicated by American Diabetes Association criteria were calculated for men and for pre- and postmenopausal women.

RESULTS—Compared with premenopausal women, women after natural menopause had an age-adjusted OR of 1.40 (95% CI 1.03–1.89) for diabetes, and women after menopause by surgical or other causes had an age-adjusted OR of 1.59 (1.07–2.37). The age-adjusted OR in men was 4.02 (3.15–5.14). Compared with premenopausal nondiabetic women, postmenopausal nondiabetic women had a significantly elevated OR of 1.33 (1.20–1.48) for prediabetes; nondiabetic men had an OR of 1.93 (1.77–2.10) independently of age and demographic and metabolic factors. Even among women aged <50 years, postmenopausal status was significantly associated with an elevated OR (1.50 [1.18–1.91]) for dysglycemia (either diabetes or prediabetes). Postmenopausal women aged ≥50 years had a particularly elevated OR for dysglycemia, regardless of age at menopause.

CONCLUSIONS—The postmenopausal state was significantly associated with the presence of dysglycemia independently of normal aging, although the increased probability in postmenopausal women did not equal that in men. Among women, menopause and older age might additively influence the elevated probability of dysglycemia.

Diabetes Care 36:4007–4014, 2013

Questions remain about why women after menopause have an increased risk of diabetes compared with men in the same age-group. The prevalence of diabetes was reported to be lower in women than in men aged ≤60 years, whereas women in their 60s and 70s were more likely to have diabetes than

men of the same age (1,2), suggesting that the hormonal changes that characterize menopause might be associated with the risk of diabetes in women after menopause (3). Although the association of menopausal status and hyperglycemia has been investigated (4–12), findings about whether the postmenopausal state would influence hyperglycemia independently of normal aging remain controversial. Two cohort studies with a large number of female participants investigated the impact of the postmenopausal state on diabetes compared with the premenopausal state (13,14). A study of 22,426 Japanese women suggested that there is no significant association between the postmenopausal state and diabetes when adjustment is made for chronological age (14). However, the other cross-sectional study of Italian women showed a positive association between spontaneous menopause and diabetes independently of age and demographic factors (13). A review indicated that neither natural nor surgical menopause per se has a strong association with diabetes risk (15).

Weight gain, which commonly occurs during the menopausal transition, seems to be attributable to aging rather than to the menopausal transition itself (3,16). However, menopause is associated with changes in body composition, such as increased total body fat or abdominal fat and a decrease in lean body mass, which in turn are linked to impairments in glucose metabolism and insulin sensitivity (3). The occurrence of dysglycemia may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency (17). A study of Korean women showed that the prevalence rate of individuals with metabolic syndrome is markedly high in those ≥50 years of age and reached a peak in

●●●

women in their 60s (7). Nonetheless, whether menopause would be associated with hyperglycemia independently of age and these other closely related metabolic factors remains unknown. In a prospective study in Spain that included 475 women, the presence of type 2 diabetes, impaired glucose tolerance, impaired fasting glucose, and other cardiometabolic markers did not differ significantly between women who went from premenopause to postmenopause and those who did not experience menopause during a 6-year follow-up period (18). To date, the joint effect of older age and the postmenopausal state on the presence of dysglycemia has not been clarified. Additionally, a few studies investigated whether a significant association exists between menopause and hyperglycemia among women without diabetes (6,19), and the results were inconsistent.

Controversy also exists about whether early age at menopause would increase diabetes risk. A recent study of postmenopausal women found early menopause to be associated with an increased risk of developing diabetes (20). In another study, on the other hand, age at menopause was not associated with diabetes in Chinese postmenopausal women (21). Cross-sectional studies in Italy (13) and China (11) did not show a significant association of age at menopause with diabetes. It should be noted that the definition of the diagnosis of diabetes differed among these studies (11,13,20,21).

Therefore, in the present cross-sectional study of Japanese individuals, we aimed to investigate whether menopause among women is associated with dysglycemia independently of normal aging and the possible mechanism whereby women after menopause would have a higher probability of having dysglycemia compared with men of a similar age. We also aimed to clarify the effect of age at menopause on the presence of type 2 diabetes and prediabetes in Japanese women.

RESEARCH DESIGN AND METHODS—The Toranomon Hospital Health Management Center Study included a cohort comprising mainly apparently healthy government employees who underwent an annual health screening in Tokyo, Japan. A total of 41,931 individuals underwent a health examination from 1997 to 2007. Routine health checkups are common in Japan because the Japanese government and companies encourage people to

receive periodic examinations. Among the 41,931 individuals, this cross-sectional study included 41,700 individuals for whom data on sex and menopausal status were available (6,458 premenopausal women, 5,701 postmenopausal women, and 29,541 men). Among those 41,700 individuals, we excluded 1,027 women who did not report a cause for menopause (natural, surgical, or other). After the exclusions, 40,673 individuals (6,458 premenopausal women, 3,630 women in natural menopause, 943 women in surgical menopause, 101 postmenopausal women by other causes, and 29,541 men) were available for analysis. We excluded 81 women aged ≥65 years who had been in the premenopausal category because their persistent vaginal bleeding after the age 65 was not likely a result of menses but of pathologic processes (12). We also excluded individuals with missing data on characteristics of lifestyle habits or clinical measures. Subsequently, 40,067 individuals (6,308 premenopausal women, 3,552 women in natural menopause, 1,018 women in surgical menopause or another cause, and 29,189 men) were included in the current analysis. With regard to women with missing data on age at menopause (n = 154), we excluded them only for the analysis of the relationship between age at menopause and dysglycemia. The study protocol followed the Japanese government's *Ethical Guidelines Regarding Epidemiological Studies* in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board at Toranomon Hospital.

Diagnosis of type 2 diabetes and prediabetes
Diagnosis of type 2 diabetes was made according to American Diabetes Association criteria (22) of a fasting plasma glucose (FPG) level ≥7.0 mmol/L (≥126 mg/dL), self-reported clinician-diagnosed diabetes or the use of hypoglycemic agents or insulin, or HbA$_{1c}$ ≥6.5% (48 mmol/mol). Prediabetes was indicated by an FPG of 5.6–6.9 mmol/L (100–125 mg/dL) or an HbA$_{1c}$ of 5.7–6.4% (39–46 mmol/mol) (22) without type 2 diabetes. Dysglycemia was indicated by the presence of either prediabetes or type 2 diabetes.

Assessment of the menopausal state and other variables
We assessed the menopausal status of women with a self-report questionnaire at the time of the examination. Female

participants were asked whether they were in a postmenopausal state. If so, they were asked to indicate the reason for menopause (natural, surgical, or other) and the age at which menopause occurred (≤39, 40–44, 45–49, or ≥50 years). Parental history of diabetes, smoking habit (never, former, or current), physical activity habit (any physical activity for 20–30 min or longer at least once weekly), and self-reported history of medical treatment for hypertension or diabetes were also assessed by the questionnaire for both men and women.

Clinical measurements
Weight and height were measured, and BMI was calculated. Blood samples were collected after an overnight fast (12 h), and measurements were made with an automatic clinical chemistry analyzer. Blood glucose concentrations were measured by enzymatic methods, and HbA$_{1c}$ was assessed by high-performance liquid chromatography. The value for HbA$_{1c}$ (%) was estimated as the National Glycohemoglobin Standardization Program value (%) calculated by Eq. 1: HbA$_{1c}$ (%) = HbA$_{1c}$ (Japan Diabetes Society) (%) × 1.02 + 0.25% (23).

Statistical analysis
Logistic regression analysis was performed to calculate odds ratios (ORs) and 95% CIs. We initially investigated whether there was a difference in the association of dysglycemia between men and women and then calculated ORs for dysglycemia for postmenopausal women (regardless of cause) and for men, with premenopausal women as the reference group. After that, we assessed whether there was a difference in the association according to cause of menopause. Because few women reported an age at menopause of <39 years, we categorized age at menopause into three groups (<45, 45–49, and ≥50 years) for the analysis. To investigate effect modifications, we performed logistic regression analysis with adjustment for age (model 1); age and other demographic factors (BMI, parental history of diabetes, physical activity habit, and smoking habit) (model 2); and age, demographic, and metabolic factors (hypertension indicated by systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or medical treatment and HDL cholesterol and log-transformed triglyceride levels) (model 3). We also examined whether a significant association existed between menopause and prediabetic

©

89

hyperglycemia among nondiabetic individuals after excluding those with type 2 diabetes.

In an additional analysis, we stratified women according age at the time of examination (<50 or ≥50 years) because the mean age of menopause has been considered to be ~50 years (9,11,14,21,24,25). A combined effect of older age at the time of the examination and the postmenopausal condition on the presence of dysglycemia (either prediabetes or type 2 diabetes) was assessed, with premenopausal women aged <50 years as the reference group. We then conducted a stratified analysis based on age at the time of examination (<50 or ≥50 years) and calculated ORs for dysglycemia across categories of age at menopause, with the premenopausal state as the reference group for women aged <50 or ≥50 years. Analysis was performed with IBM SPSS Statistics version 19 (IBM, Armonk, NY). Statistical significance was considered for $P < 0.05$.

RESULTS—Mean (SD) age was 48.4 (9.9) years among the 10,878 women

studied and 48.0 (9.7) years among the 29,189 men studied (Table 1). Of the 10,878 women, 2,340 (21.5%) had prediabetes and 246 (2.3%) had type 2 diabetes. Premenopausal women were younger (42.1 [6.6] years) compared with postmenopausal women. We did not observe a marked difference in BMI between premenopausal and postmenopausal women. Among the premenopausal women, only 69 (1.1%) had type 2 diabetes, whereas the prevalence rate was high at 3.8% in women after natural menopause and 4.0% after surgical menopause or menopause from other causes. More than one in three of the postmenopausal women and the men had either prediabetes or type 2 diabetes.

Table 2 shows ORs for type 2 diabetes and prediabetes among men and among women by menopausal status. Men were 2.10 (95% CI 1.81–2.45) times more likely to have type 2 diabetes than the total number of women studied according to multivariate model 3, which included age and demographic and metabolic factors. Postmenopausal

women had a significant association with type 2 diabetes (1.36 [1.01–1.82]) compared with premenopausal women that was independent of age, BMI, smoking habit, physical activity habit, and parental history of diabetes (model 2), although the OR was not as high as that in men (2.87 [2.23–3.69]). After adjustment for lipid measurements and hypertension (model 3), the OR for the postmenopausal women was attenuated (1.17 [0.88–1.58]), and a significant association with the presence of type 2 diabetes remained only among the men (2.35 [1.82–3.03]). Among the women, we did not find an obvious difference in the association of type 2 diabetes and menopausal status regardless of the cause of menopause. The association of prediabetes with menopause among individuals without type 2 diabetes showed that postmenopausal women had a significantly elevated OR for prediabetes in model 3 (1.33 [1.20–1.48]) compared with premenopausal women. Additionally, the men had a significantly elevated OR for prediabetes compared with

Table 1—*Characteristics of total women, premenopausal women, postmenopausal women (by cause), and men*

	Total women	Premenopausal women	Postmenopausal women		Men
			Natural	Surgical or other cause	
No. participants	10,878	6,308	3,552	1,018	29,189
Age (years)	48.4 (9.9)	42.1 (6.6)	57.5 (6.2)	55.6 (7.7)	48.0 (9.7)
BMI (kg/m²)	21.6 (3.1)	21.5 (3.1)	21.8 (3.0)	22.1 (3.1)	23.5 (2.9)
Parental diabetes	1,802 (16.6)	1,097 (17.4)	539 (15.2)	166 (16.3)	4,237 (14.5)
Physical activity (yes)	4,828 (44.4)	2,548 (40.4)	1,792 (50.5)	488 (47.9)	13,791 (47.2)
Smoking habit					
Never	9,131 (83.9)	5,193 (82.3)	3,084 (86.8)	854 (83.9)	12,132 (41.6)
Former	680 (6.3)	427 (6.8)	189 (5.3)	64 (6.3)	7,953 (27.2)
Current	1,067 (9.8)	688 (10.9)	279 (7.9)	100 (9.8)	9,104 (31.2)
Age at menopause					
<45 years	—	—	181 (5.1)	479 (47.1)	—
45–49 years	—	—	997 (28.1)	293 (28.8)	—
≥50 years	—	—	2,303 (64.8)	163 (16.0)	—
Missing data	—	—	71 (2.0)	83 (8.2)	—
Hypertension*	1,560 (14.3)	512 (8.1)	793 (22.3)	255 (25.0)	6,673 (22.9)
HDL cholesterol (mmol/L)	1.64 (0.36)	1.63 (0.34)	1.65 (0.39)	1.61 (0.37)	1.33 (0.34)
Triglycerides (mmol/L)	0.79 (0.60, 1.08)	0.72 (0.55, 0.97)	0.90 (0.68, 1.22)	0.93 (0.70, 1.28)	1.22 (0.87, 1.77)
FPG (mmol/L)	5.1 (0.7)	5.0 (0.6)	5.3 (0.8)	5.3 (0.7)	5.5 (1.0)
HbA$_{1c}$ (%)	5.3 (0.5)	5.2 (0.4)	5.5 (0.5)	5.4 (0.6)	5.4 (0.7)
HbA$_{1c}$ (mmol/mol)	34 (5)	33 (5)	36 (6)	35 (6)	35 (8)
Glycemic state†					
Normoglycemia	8,292 (76.2)	5,341 (84.7)	2,274 (64.0)	677 (66.5)	17,116 (58.6)
Prediabetes	2,340 (21.5)	898 (14.2)	1,142 (32.2)	300 (29.5)	10,179 (34.9)
Type 2 diabetes	246 (2.3)	69 (1.1)	136 (3.8)	41 (4.0)	1,894 (6.5)

Data are mean (SD), n (%), or median (25th, 75th percentile). *Hypertension was indicated by systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or medical treatment. †Normoglycemia was indicated by FPG <5.6 mmol/L and HbA$_{1c}$ <5.7% (39 mmol/mol) without type 2 diabetes; prediabetes was indicated by FPG 5.6–6.9 mmol/L or HbA$_{1c}$ 5.7–6.4% (39–46 mmol/mol) without type 2 diabetes; and type 2 diabetes was indicated by FPG ≥7.0 mmol/L or HbA$_{1c}$ ≥6.5% (48 mmol/mol) or self-reported history of clinician-diagnosed diabetes or the use of hypoglycemic agents or insulin.

Table 2—ORs (95% CI) for type 2 diabetes or prediabetes between women and men (A), among pre- or postmenopausal women and men (B and C), or among pre- or postmenopausal women according to age at menopause and men (D)

	Type 2 diabetes				Prediabetes			
	Cases/total	Model 1	Model 2	Model 3	Cases/total	Model 1	Model 2	Model 3
A								
Women	246/10,878	1	1	1	2,340/10,632	1	1	1
Men	1,894/29,189	3.15 (2.75–3.61)	2.34 (2.02–2.71)	2.10 (1.81–2.45)	10,179/27,295	2.26 (2.14–2.38)	1.77 (1.67–1.88)	1.67 (1.56–1.77)
B								
Premenopausal women	69/6,308	1	1	1	898/6,239	1	1	1
Postmenopausal women	177/4,570	1.44 (1.08–1.92)	1.36 (1.01–1.82)	1.17 (0.88–1.58)	1,442/4,393	1.51 (1.37–1.68)	1.47 (1.32–1.63)	1.33 (1.20–1.48)
Men	1,894/29,189	4.02 (3.15–5.14)	2.87 (2.23–3.69)	2.35 (1.82–3.03)	10,179/27,295	2.79 (2.58–3.01)	2.15 (1.99–2.34)	1.93 (1.77–2.10)
C								
Premenopausal women	69/6,308	1	1	1	898/6,239	1	1	1
Postmenopausal women (natural)	136/3,552	1.40 (1.03–1.89)	1.34 (0.99–1.82)	1.17 (0.86–1.59)	1,142/3,416	1.53 (1.37–1.70)	1.50 (1.35–1.67)	1.36 (1.22–1.52)
Postmenopausal women (surgical or other cause)	41/1,018	1.59 (1.07–2.37)	1.42 (0.95–2.13)	1.20 (0.80–1.80)	300/977	1.46 (1.25–1.71)	1.36 (1.16–1.60)	1.22 (1.04–1.43)
Men	1,894/29,189	4.02 (3.15–5.14)	2.87 (2.23–3.69)	2.35 (1.82–3.03)	10,179/27,295	2.79 (2.58–3.01)	2.15 (1.99–2.34)	1.93 (1.77–2.10)
D								
Premenopausal women	69/6,308	1	1	1	898/6,239	1	1	1
Postmenopausal women by age at menopause								
<45 years	29/660	1.89 (1.21–2.96)	1.73 (1.10–2.73)	1.49 (0.94–2.35)	177/631	1.37 (1.13–1.66)	1.31 (1.08–1.60)	1.20 (0.98–1.46)
45–49 years	43/1,290	1.29 (0.87–1.91)	1.24 (0.84–1.85)	1.09 (0.73–1.62)	389/1,247	1.46 (1.27–1.69)	1.44 (1.24–1.67)	1.31 (1.13–1.52)
≥50 years	98/2,466	1.39 (1.01–1.92)	1.32 (0.95–1.82)	1.14 (0.82–1.57)	831/2,368	1.59 (1.42–1.79)	1.55 (1.37–1.74)	1.39 (1.23–1.57)
Men	1,894/29,189	4.02 (3.15–5.14)	2.86 (2.23–3.68)	2.34 (1.82–3.02)	10,179/27,295	2.79 (2.58–3.01)	2.15 (1.98–2.33)	1.93 (1.77–2.09)

Model 1, age; model 2, age, BMI, parental history of diabetes, smoking habit (never, former, current), and physical activity habit; model 3, age, BMI, parental history of diabetes, smoking habit, physical activity habit, hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or medical treatment), log-transformed triglyceride levels, and HDL cholesterol level. Data in boldface are statistically significant.

postmenopausal women (1.93 [1.77–2.10]). Regardless of age or demographic or metabolic factors, women with natural menopause or other causes of menopause had similarly elevated ORs for prediabetes (1.36 [1.22–1.52] and 1.22 [1.04–1.43], respectively). We observed that early age at menopause (<45 years) was significantly associated with an elevated OR for diabetes after adjustment for age (1.89 [1.21–2.96]) or for age and demographic factors (1.73 [1.10–2.73]). This association was not significant after adjustment for hypertension and lipid measurements (model 3). We did not observe an association of early menopause with an increased probability of having prediabetes among individuals without type 2 diabetes.

Figure 1 shows the combined effect of age at examination and menopausal status on the presence of dysglycemia (either prediabetes or type 2 diabetes). Although older age alone at the time of the examination (≥50 years) was significantly associated with dysglycemia (OR 2.21 [95% CI 1.85–2.65]), postmenopausal status alone was also significantly associated with an elevated OR for dysglycemia (1.50 [1.18–1.91]). The postmenopausal condition and older age additively influenced an elevated OR because postmenopausal women aged ≥50 years had a markedly elevated OR (3.69 [3.34–4.08]) for dysglycemia. We stratified women by age at the time of the examination and investigated whether there was an association of age at menopause with the presence of dysglycemia (Table 3). Compared with premenopausal women, postmenopausal women who underwent menopause at <45 or 45–49 years had a 1.41 (0.98–2.02) and 1.59 (1.15–2.20) times increased OR for dysglycemia, respectively, even among women aged <50 years at the time of examination (n = 5,991). Adjustment for demographic and metabolic factors (multivariate model 2) attenuated the ORs (1.18 [0.80–1.74] and 1.29 [0.91–1.82], respectively). Among women aged ≥50 years, the postmenopausal state was significantly associated with the presence of dysglycemia, regardless of age at which menopause occurred. In multivariate model 2, postmenopausal women had a similarly elevated OR for dysglycemia to premenopausal women, regardless of age at menopause (<45 years of age 1.58 [1.22–2.04], 45–49 years of age 1.62 [1.31–2.00], ≥50 years of age 1.65 [1.37–1.99]).
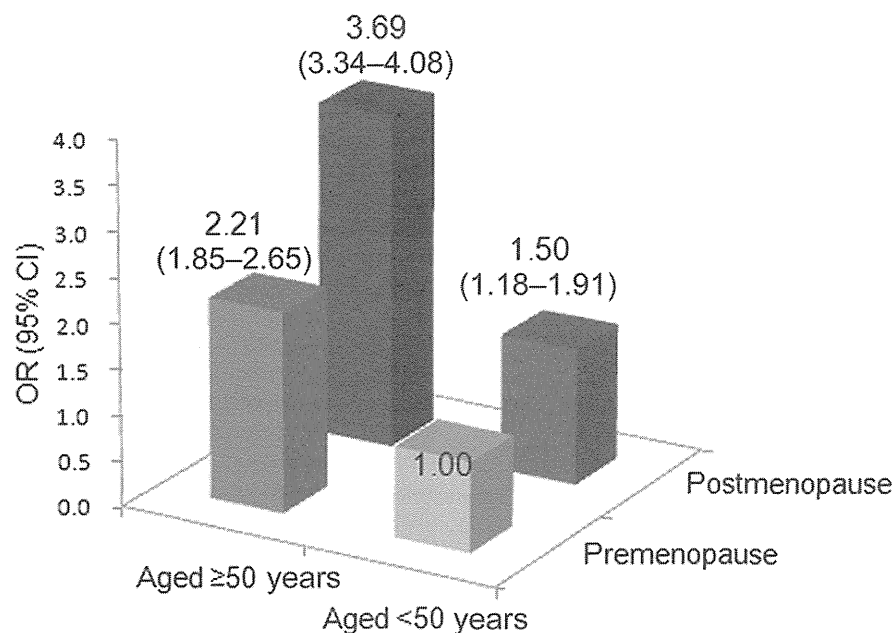
91

Figure 1—*Probability of having dysglycemia (either prediabetes or type 2 diabetes) through a combination of age at the time of examination and menopausal status. Data are crude OR and 95% CI.*

CONCLUSIONS—We found that older age and a postmenopausal state independently and additively influenced the high prevalence of dysglycemia in Japanese women. Even among women aged <50 years at the time of examination, menopause was associated with the presence of dysglycemia. The study is unique because it compared the probability of dysglycemia among women across menopausal states with that among mainly middle-aged men who underwent health screening in Japan. Although the OR for postmenopausal women was not high compared with that of the men, their ORs for type 2 diabetes and prediabetes were significantly elevated independently of age compared with those in premenopausal women.

Whether menopausal status would influence the occurrence of diabetes independently of age and other confounding factors remains controversial because it is difficult to conduct studies to separate the effects of normal aging from the menopausal transition. A few studies showed a significant positive association of hyperglycemia with menopausal status after adjustment for age and other risk factors for diabetes (7,13,19), but multivariate analyses in other studies showed no such associations (4,11,14,18,26). In a cross-sectional multicenter study of Italian women from outpatient menopausal clinics, those with natural menopause had a 1.38 times

higher multivariate-adjusted OR for diabetes than premenopausal women (13). On the other hand, the researchers did not find a significant association in women with surgical menopause and diabetes (13). A cross-sectional study of Korean women suggested that in postmenopausal women, there is a significant association with the presence of hyperglycemia (fasting glucose level ≥110 mg/dL or anti-diabetes medications) compared with premenopausal women that is independent of age and BMI (7). In women at high risk for diabetes who participated in the Diabetes Prevention Program, no association was found between natural menopause or bilateral oophorectomy and increased risk of developing diabetes after adjustment for age (12). Another influence of the controversy might be that assessment of the menopausal state usually is based on self-reported responses or interviews and that participant characteristics vary among studies. The present study shows a significant positive association between postmenopause (regardless of cause) and the presence of type 2 diabetes independently of normal aging compared with premenopause. However, we did not include oral glucose tolerance test (OGTT) data in the diagnosis of diabetes. Diabetes and impaired fasting glycemia are reported to be more common in men than in women 30–69 years of age, whereas the prevalence of isolated postload

hyperglycemia, particularly impaired glucose tolerance, is reportedly higher in women than in men, especially in individuals >70 years of age (27). Additionally, impaired glucose tolerance is more prevalent than impaired fasting glycemia in Asian populations for all age-groups (28). The lack of data on OGTT for the diagnosis of dysglycemia might lead to an underestimation of the associations between menopause and the prevalence of diabetes. Further prospective studies that include OGTT data are needed to confirm the current findings.

The significant association of type 2 diabetes and postmenopausal status was particularly attenuated after adjustments for hypertension and blood lipid measurements, suggesting that when we consider the association of menopause with diabetes, we also should consider the influence of related metabolic factors. Because the transition from the premenopausal to the postmenopausal state is associated with changes in body composition (increased body fat mass, increased abdominal fat, and decreased lean body mass) (3) and substantial metabolic changes, features of metabolic syndrome would occur in many women (17). More recent research, however, suggested that postmenopausal women have higher levels of adiposity, but the association was predominantly a result of aging (29). Another recent study raised the possibility that even if body composition changes with the menopausal transition, these changes are not accompanied by cardiometabolic deterioration during a relatively short follow-up period (30). Because data on body composition or visceral fat were not available for the current study, we could not assess whether differences in body composition across the menopausal state might have influenced the presence of dysglycemia, even if BMIs across the menopausal state were relatively low. Asians are more likely to have a higher percentage of fat or visceral adipose tissue at a given BMI than Europeans (31). This ethnic difference regarding the obese phenotype might increase insulin resistance, leading to impaired glucose metabolism. Although we did not have data on reproductive hormone concentrations and cannot explain the mechanism for the current observations, it was shown that natural menopause is characterized by increased relative androgenicity, which was reported to be associated with glucose metabolism (15); furthermore, reproductive hormone

Table 3—*Association of dysglycemia (either prediabetes or type 2 diabetes) and age at menopause among women aged <50 or ≥50 years at the time of examination*

	Premenopausal state	Postmenopausal state by age at menopause		
		<45 years	45–49 years	≥50 years
Among women aged <50 years at the time of examination (n = 5,991)				
Cases/total (n)	768/5,549	38/206	48/236	N/A
Unadjusted model	1.00	1.41 (0.98–2.02)	1.59 (1.15–2.20)	N/A
P value	—	0.063	0.005	N/A
Multivariate model 1	1.00	1.30 (0.89–1.90)	1.54 (1.09–2.15)	N/A
P value	—	0.171	0.013	N/A
Multivariate model 2	1.00	1.18 (0.80–1.74)	1.29 (0.91–1.82)	N/A
P value	—	0.401	0.157	N/A
Among women aged ≥50 years at the time of examination (n = 4,733)				
Cases/total (n)	199/759	168/454	384/1,054	929/2,466
Unadjusted model	1.00	1.65 (1.29–2.12)	1.61 (1.31–1.98)	1.70 (1.42–2.04)
P value	—	<0.001	<0.001	<0.001
Multivariate model 1	1.00	1.74 (1.35–2.25)	1.75 (1.42–2.15)	1.81 (1.50–2.17)
P value	—	<0.001	<0.001	<0.001
Multivariate model 2	1.00	1.58 (1.22–2.04)	1.62 (1.31–2.00)	1.65 (1.37–1.99)
P value	—	<0.001	<0.001	<0.001

Data are OR (95% CI) unless otherwise indicated. Multivariate model 1, BMI, parental history of diabetes, smoking habit (never, former, current), and physical activity habit; multivariate model 2, model 1 + hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or medical treatment), log-transformed triglycerides, and HDL cholesterol level. N/A, not applicable.

concentrations can vary by ethnicity and were shown to be confounded by ethnic disparities in body mass (32). Further studies should investigate mechanisms that link menopause and diabetes with detailed assessments of body composition, insulin sensitivity, insulin secretion, and reproductive hormone concentrations in perimenopausal women across various ethnic groups to confirm the current findings.

The current results show that among individuals without diabetes, prediabetic hyperglycemia is significantly associated with postmenopausal status independently of age and demographic and metabolic parameters. In a cross-sectional study of Japanese women without diabetes, stepwise regression analysis showed natural menopause rather than age as a significant determinant of FPG concentrations (19). On the other hand, among middle-aged women living in North Taiwan, no significant difference in FPG, insulin levels, homeostasis model assessment of insulin resistance, and prevalence of hyperglycemia between premenopausal and postmenopausal women was shown (6). The current results show that prediabetic hyperglycemia and the postmenopausal state are positively associated, suggesting that postmenopausal women might be at high risk for diabetes.

In a prospective case-cohort study that included only postmenopausal women, earlier age at menopause was associated with a greater risk of type 2 diabetes (20). The hazard ratio for diabetes was 32% higher in women who entered menopause before 40 years of age compared with those experiencing menopause at age 50–54 (20). A study in Chinese postmenopausal women, however, showed no association between age at menopause and diabetes (21). The results of the current cross-sectional investigation suggest that early age at menopause (<45 years) might be more strongly associated with type 2 diabetes than menopause at ≥50 years. Nonetheless, regardless of age at menopause, postmenopausal women aged ≥50 years at the time of the examination had an ~1.5 times increased probability of having dysglycemia compared with premenopausal women. Some differences exist in age at menopause onset across ethnic groups (25). Additionally, age at menopause can be affected by various social and environmental factors (25,33), which might be one possible explanation for the mixed results of the association of age at menopause and diabetes compared with existing studies. It has been established that a smoking habit is significantly associated with an early age at natural menopause

(34). Factors of lower educational attainment; being separated, widowed, or divorced; and nonemployment have been associated with early natural menopause, whereas Japanese ethnicity is associated with late age at natural menopause (33). Furthermore, BMI has been associated with age at menopause (35). On the other hand, a recent study of women from five racial and ethnic groups indicated that there is no significant racial/ethnic difference in age at the final natural menstrual cycle after controlling for sociodemographic, lifestyle, and health factors (36). Further prospective investigations are needed to assess whether early menopause would increase the risk of developing diabetes across various ethnic groups while considering differences in demographic factors among study participants.

Recent reports indicated that early age at natural menopause is associated with an increased risk of ischemic stroke (37) and mortality (38). Nonetheless, both menopause and aging are nonmodifiable factors. Regular physical activity may help to mitigate the tendency for weight gain and adverse changes in body composition and fat distribution that accompany aging and the menopausal transition (39). High levels of habitual physical activity, such as walking, have been associated with a favorable

cardiovascular risk profile in postmenopausal women (40). Further investigations are needed on whether different interventions for older postmenopausal women could control modifiable factors such as metabolically unhealthy obesity, dyslipidemia, hypertension, and lifestyle.

We recognize several limitations in this study. The study participants were relatively lean, apparently healthy Japanese government employees who underwent a routine health examination. Thus, these individuals were more likely to pay attention to healthy lifestyle habits than those who did not have such an examination. The characteristics of the study participants, such as BMI and cardiometabolic factors, would influence the generalizability of the findings, although we analyzed these factors in multivariate models. The generalizability of the results should be validated in various other populations. Additionally, limitations of the available data prevented a more in-depth analysis of factors that could influence an increased risk of developing diabetes; therefore, we cannot rule out the possibility that residual confounding influenced the results. Because we did not include data on nutritional intake or other known risk factors for diabetes, such as sleep disturbances and depression, which are commonly observed in women at midlife, we could not adjust the results for the influence of such factors. We did not have data on visceral fat or hormone replacement therapy, so that the ORs might be over- or underestimated. Nonetheless, the prevalence of women receiving hormone replacement therapy is considered to be low in Japan. Because the assessment of menopausal status is based on self-report, we cannot deny the possibility of misclassification of menopausal status among the women studied.

In conclusion, in this study of a large number of female and male Japanese individuals, the postmenopausal state in women was significantly associated with the presence of type 2 diabetes and prediabetes, although the increased probability did not equal that in the men. The postmenopausal state was also associated with prediabetic hyperglycemia independently of age and demographic and metabolic factors among women without diabetes. Menopause and older age might additively influence the elevated probability of dysglycemia in Japanese women.

References
1. Yang W, Lu J, Weng J, et al.; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010;362:1090–1101
2. International Diabetes Federation. *Diabetes Atlas*. 5th ed. Brussels, International Diabetes Federation, 2011
3. Szmuilowicz ED, Stuenkel CA, Seely EW. Influence of menopause on diabetes and diabetes risk. Nat Rev Endocrinol 2009;5:553–558
4. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 2007;30:701–706
5. Wu SI, Chou P, Tsai ST. The impact of years since menopause on the development of impaired glucose tolerance. J Clin Epidemiol 2001;54:117–120
6. Lin WY, Yang WS, Lee LT, et al. Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and postmenopausal women in North Taiwan. Int J Obes (Lond) 2006;30:912–917
7. Cho GJ, Lee JH, Park HT, et al. Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause 2008;15:524–529
8. Feng Y, Hong X, Wilker E, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis 2008;196:590–597
9. Park HA, Park JK, Park SA, Lee JS. Age, menopause, and cardiovascular risk factors among Korean middle-aged women: the 2005 Korea National Health and Nutrition Examination Survey. J Womens Health (Larchmt) 2010;19:869–876
10. Zivkovic TB, Vuksanovic M, Jelic MA, et al. Obesity and metabolic syndrome during the menopause transition in Serbian women. Climacteric 2011;14:643–648
11. He L, Tang X, Li N, et al. Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: a population-based study. Maturitas 2012;72:132–138
12. Kim C, Edelstein SL, Crandall JP, et al.; Diabetes Prevention Program Research Group. Menopause and risk of diabetes in the Diabetes Prevention Program. Menopause 2011;18:857–868
13. Di Donato P, Giulini NA, Bacchi Modena A, et al.; Gruppo di Studio Progetto Menopausa Italia. Risk factors for type 2 diabetes in women attending menopause clinics in Italy: a cross-sectional study. Climacteric 2005;8:287–293
14. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses' health study. J Atheroscler Thromb 2013;20:161–169
15. Kim C. Does menopause increase diabetes risk? Strategies for diabetes prevention in midlife women. Womens Health (Lond Engl) 2012;8:155–167
16. Davis SR, Castelo-Branco C, Chedraui P, et al.; Writing Group of the International Menopause Society for World Menopause Day 2012. Understanding weight gain at menopause. Climacteric 2012;15:419–429

17. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88:2404–2411
18. Soriguer F, Morcillo S, Hernando V, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause 2009;16:817–821
19. Otsuki M, Kasayama S, Morita S, et al. Menopause, but not age, is an independent risk factor for fasting plasma glucose levels in nondiabetic women. Menopause 2007;14:404–407
20. Brand JS, van der Schouw YT, Onland-Moret NC, et al.; InterAct Consortium. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. Diabetes Care 2013; 36:1012–1019
21. Qiu C, Chen H, Wen J, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. J Clin Endocrinol Metab 2013; 98:1612–1621
22. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
23. Kashiwagi A, Kasuga M, Araki E, et al.; Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society (JDS). International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. Diabetology Int 2012;3:8–10
24. Nelson HD. Menopause. Lancet 2008; 371:760–770
25. Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P. Age of menopause and impact of climacteric symptoms by geographical region. Climacteric 2010; 13:419–428
26. Monterrosa-Castro A, Blümel JE, Portela-Buelvas K, et al.; Collaborative Group for Research of the Climacteric in Latin America (REDLINC). Type II diabetes mellitus and menopause: a multinational study. Climacteric. 6 June 2013 [Epub ahead of print]
27. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61–69
28. Qiao Q, Hu G, Tuomilehto J, et al.; DECODA Study Group. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care 2003;26:1770–1780
29. Trikudanathan S, Pedley A, Massaro JM, et al. Association of female reproductive factors with body composition: the Framingham Heart Study. J Clin Endocrinol Metab 2013;98:236–244
30. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause 2012;19:760–767
31. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2012;8:228–236
32. Randolph JF Jr, Sowers M, Gold EB, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. J Clin Endocrinol Metab 2003;88: 1516–1522
33. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001; 153:865–874
34. Sun L, Tan L, Yang F, et al. Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. Menopause 2012;19:126–132
35. Akahoshi M, Soda M, Nakashima E, et al. The effects of body mass index on age at menopause. Int J Obes Relat Metab Disord 2002;26:961–968
36. Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 2013;178:70–83
37. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. Stroke 2009;40:1044–1049
38. Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol 2006; 16:161–166
39. Sternfeld B, Bhat AK, Wang H, Sharp T, Quesenberry CP Jr. Menopause, physical activity, and body composition/fat distribution in midlife women. Med Sci Sports Exerc 2005;37:1195–1202
40. Colpani V, Oppermann K, Spritzer PM. Association between habitual physical activity and lower cardiovascular risk in premenopausal, perimenopausal, and postmenopausal women: a population-based study. Menopause 2013;20:525–531

©

日本人2型糖尿病患者の特徴と病態についての臨床疫学

曽根 博仁　　赤沼 安夫　　山田 信博

日本人2型糖尿病患者の特徴と病態についての臨床疫学

曽根 博仁[1]　赤沼 安夫[2]　山田 信博[3]

要　旨

2型糖尿病は遺伝背景や生活習慣・環境が深く関与することから，その臨床像に大きな人種・民族差(ethnic differences)が存在する．これは基礎的病態から各合併症のリスク因子に至るまで多岐にわたり，たとえばインスリン分泌能やインスリン抵抗性と関連する肥満度は，わが国の患者では欧米人患者より大幅に低い．さらにわが国に多い喫煙が腎症のリスク因子であったり，わが国で少ない果物摂取量と網膜症発症が有意に関連していたりなど，生活習慣との関連も見られる．したがって診療ガイドラインを作成したり，大規模臨床エビデンスを実地診療に適用したりする際には，これらの違いについて十分な配慮が必要である．日本人に最適化された糖尿病予防・治療対策の確立のためには，日本人における大規模臨床研究をさらに推進しデータを集積していく必要がある．

〔日内会誌　102：2714〜2722，2013〕

Key words　腎症，網膜症，大血管症，人種差，リスク因子

1. 2型糖尿病の人種・民族差

国民健康・栄養調査によると，疑い例を含めた糖尿病患者は40歳以上の国民3人に1人を占め，まさに国民病といっても過言ではない状況である．糖尿病の95%以上を占める2型糖尿病の病態や臨床像は遺伝的背景や生活習慣の影響を強く受けることから，大きな人種・民族差(ethnic differences)が存在することが知られている．

2型糖尿病では，インスリン作用低下を基盤とした慢性的高血糖，血清脂質異常，高血圧など多くの代謝障害が見られる．このインスリン作用低下は，インスリン分泌能低下とインスリン抵抗性増大(インスリン感受性低下とも言う)のいずれによってももたらされるが，両者の寄与度の割合が，白人・黒人・ヒスパニック系などを中心とした欧米人と日本人を含む東アジア人とではかなり異なる．このことは両地域の2型糖尿病患者の肥満度によく表れており，日本人

は欧米人よりかなり軽度の肥満でも糖尿病を発症しやすい上, 糖尿病発症後の平均肥満度も欧米人よりかなり低く, 「痩せているのに高血糖」の高齢患者が多くなる. これは日本人のインスリン分泌予備能が欧米人より平均的に低く, 高齢化, 罹病期間長期化によってさらに低下しやすいためと考えられる. この点は発症後10年を経ても, 一般住民と比して平均的にかなり肥満している欧米人糖尿病患者との大きな違いであり[1], 薬物の効果などにも影響を与えうる点である[2].

2. 日本人2型糖尿病患者のエビデンスの必要性

これまで内外の糖尿病診療ガイドラインの根拠となってきたエビデンスの多くは, 欧米人対象の大規模臨床研究から得られたものであり, それらのすべてが基本的病態の大きく異なる日本人患者にあてはまるとは限らない[3]. したがってわが国の大規模臨床研究を推進し, そこから得られたエビデンスによりわが国の糖尿病患者に適した診療体系を構築することが望ましいと考えられる. 近年, わが国の糖尿病大規模臨床エビデンスは次第に増加しているが, 本稿では紙数の関係もあり, 臨床エビデンスが欧米一辺倒であった時代から東アジア人特有の2型糖尿病患者の特徴を世界に発信してきたJapan Diabetes Complications Study (JDCS) を中心にその一部を紹介する.

3. Japan Diabetes Complications Study (JDCS) の意義と概要

Japan Diabetes Complications Study (JDCS) は, 欧米以外では最も早く始められた2型糖尿病患者対象の大規模臨床研究の一つであり, 日本人糖尿病患者の特徴を明らかにすると同時に,

生活習慣療法を中心にした強化治療の合併症予防効果を検討しつつ現在に至っている. 1996年に始まった本研究は, 全国59カ所の糖尿病専門施設(主に大学病院や総合病院の糖尿病科)外来に通院中の, 進行合併症を持たない日本人2型糖尿病患者約2,033名(平均59歳, 女性47%)を対象にした大規模臨床研究である. 参加施設の先生方の長年の努力により, 対象者の血糖・血圧・血清脂質・生活習慣などの臨床検査と合併症の発症・進展に関するデータを収集してきた.

4. 腎症とそのリスク因子

JDCS登録時に正常アルブミン尿 (ACR<30 mg/g Cre) であった患者における, 顕性腎症 (ACR≧300 mg/g CRE)発症率は1,000人あたり年間2.3人と欧米諸国と比較してもかなり少なかった[4]. さらに早期腎症 (ACR 30～299 mg/g Cre) のうち比較的軽症 (ACR 30～150 mg/g Cre) の者については, 8年間で約30%に寛解 (ACR<30 mg/g Creへの正常化) がみられ, わが国の専門医に管理された糖尿病患者では, 腎症の進行がかなり抑制されている可能性が示唆された.

一方, 比較的軽度であっても登録時すでに微量アルブミン尿 (ACR 30～150 mg/g Cre) を有していた患者の顕性腎症発症リスクは, 正常アルブミン尿患者の8.5倍にも上り[4], たとえ軽度でもアルブミン尿がみられた際は, 顕性腎症への進展阻止を図るべく治療を強化する必要性が示唆された. 血糖や血圧についても, HbA1c (NGSP)<7.4%の患者と比較して7.4～9.3%では2.7倍, 9.4%以上では5.8倍, 収縮期血圧<120 mmHgの患者と比較して120～139mmHgでは2.3倍, 140 mmHg以上では3.6倍のそれぞれリスク上昇がみられ, これらのコントロールの重要性も改めて明らかになった.