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ARTICLE

Leisure-time physical activity is a significant predictor of stroke and total mortality in Japanese patients with type 2 diabetes: analysis from the Japan Diabetes Complications Study (JDCS)

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Abstract
Aims/hypothesis Our aim was to clarify the association between leisure-time physical activity (LTPA) and cardiovascular events and total mortality in a nationwide cohort of Japanese diabetic patients.

Methods Eligible patients (1,702) with type 2 diabetes (mean age, 58.5 years; 47% women) from 59 institutes were followed for a median of 8.05 years. A comprehensive lifestyle survey including LTPA and occupation was performed using standardised questionnaires. Outcome was

A complete list of members of the JDCS group can be found in the electronic supplementary material (ESM).

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occurrence of coronary heart disease (CHD), stroke and total mortality. The adjusted HR and 95% CI were calculated by Cox regression analysis.
Results A significant reduction in HR in patients in the top (≥15.4 metabolic equivalents [MET] h/week) vs the bottom tertile (≤3.7 MET h/week) of LTPA, adjusted by age, sex and diabetes duration, was observed in stroke (HR 0.55, 95% CI 0.32, 0.94) and total mortality (HR 0.49, 95% CI 0.26, 0.91) but not in CHD (HR 0.77, 95% CI 0.48, 1.25). The HR for stroke became borderline significant or nonsignificant after adjustment for lifestyle or clinical variables including diet or serum lipids. The significantly reduced total mortality by LTPA was independent of these variables and seemed not to be, at least mainly, attributed to reduced cardiovascular disease.
Conclusions/interpretation In Japanese persons with type 2 diabetes, LTPA of 15.4 MET h/week or more was associated with a significantly lower risk of stroke partly through ameliorating combinations of cardiovascular risk factors. It was also associated with significantly reduced total mortality but independently of cardiovascular risk factors or events. These findings, implying differences from Western diabetic populations, should be considered in the clinical management of East Asians with diabetes.

Keywords Asian · Cardiovascular disease · Cohort study · Ethnic difference · Exercise · Macrovascular complications · Physical activity

Abbreviations

IGT	Impaired glucose tolerance
JDCS	Japan Diabetes Complications Study
JDS	Japan Diabetes Society
LTPA	Leisure-time physical activity
MET	Metabolic equivalents

Introduction

Type 2 diabetes is a significant cause of premature mortality and morbidity especially related to cardiovascular disease. Regular exercise has been recommended to prevent these diabetic complications through ameliorating control of several variables related to diabetes [1–3]. Many but not all [4–6] cohort studies have shown that physical activity is prospectively associated with reduced total [7–18] and cardiovascular [7–13, 19] mortality. It has also been demonstrated, albeit in a few studies [4, 18, 20, 21], that cardiovascular events (i.e. coronary heart disease [CHD] and stroke) were reduced according to increased physical activity in individuals with diabetes. However, only two of those studies [4, 18] analysed cardiovascular events and mortality simultaneously and produced conflicting results on mortality. In addition, only three of those studies [4, 20, 21] determined CHD and stroke separately and their results for stroke were conflicting. Therefore, it is still unclear how physical activity exerts its effect on reducing mortality in patients with diabetes and whether macrovascular complications of diabetes are reduced in accordance with increased physical activity.

Most previous studies evaluated physical activity only as non-numerical or bivariate variables, such as a self-reported response of whether exercise was done regularly [5–9, 12–14, 16, 20] or only with regard to walking [11, 19]. Data are not abundant on dose–effect relationships regarding quantity of physical activity, especially determined in units of metabolic equivalents (MET) h [15, 18, 21]. These units are universally used for quantification of physical activity and are useful for determining cut-offs in required amounts of exercise for risk reduction and exchange of values for different types of exercise and complications and mortality in patients with diabetes.

While different approaches to exercise are needed depending on ethnicity because of different responses to exercise among ethnic groups [3], all of these previous cohort studies were carried out in Western diabetic populations with only a few exceptions [4, 7]. However, it is uncertain whether results from Western diabetic patients can be extrapolated to East Asian populations with diabetes. In this analysis of data from a long-term follow-up of Japanese patients with type 2 diabetes, we analysed the association between leisure-time physical activity (LTPA), which accounts for an important part of exercise therapy for diabetic persons, and risk for CHD, stroke and total mortality.

Methods

Recruitment of patients The present analysis was conducted as part of the Japan Diabetes Complications Study (JDCS), a multicentre prospective study of the incidence of and risk factors for complications among 2,033 Japanese patients with type 2 diabetes aged 40–70 years with HbA_{1c} (Japan Diabetes Society [JDS]) levels ≥6.5% (51 mmol/mol) who were registered from January 1995 to March 1996 from outpatient clinics in 59 university and general hospitals nationwide that specialise in diabetes care. Of those 2,033 individuals, 940 men (mean age ± SD 57.8±7.1 years) and 831 women (58.7±6.8 years) were selected for the analysis of macrovascular complications after consideration of the exclusion criteria pre-specified in the study protocol [22]. Patients were excluded if they had impaired glucose tolerance (IGT), a history of angina pectoris, myocardial infarction, stroke, peripheral artery disease, familial hypercholesterolaemia, type III hyperlipidaemia (diagnosed by a broad beta band on electrophoresis) or nephrotic syndrome (urine protein >3.5 g per day and serum total protein <60 g/l) and serum creatinine levels greater than 120 μmol/l (1.3 mg/dl). In the 8-year planned observation period, the median

follow-up for the 1,771 patients was 7.86 years (final follow-up rate was 75%; 1,332/1,771 patients). For this analysis of physical activity, data on the 1,702 patients (901 men, age 58.2±7.0 years; 801 women, age 58.9±6.8 years) who responded to the baseline physical activity survey were used. There was no notable difference in baseline characteristics between responders and non-responders. We analysed follow-up data until March 2003.

Diabetes mellitus and IGT 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 thresholds for glucose levels to those of the WHO. The study protocol, 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 ethics approval from the institutional review boards of all participating institutes. All enrolled patients provided written informed consent.

Assessment of LTPA LTPA was assessed at baseline by a self-administered questionnaire, which was almost identical to that used and validated in the Health Professionals' Follow-up Study [18]. The patients were asked the average frequency (times/week) and duration (min/time) of normal walking, brisk walking, jogging, golf, tennis, swimming, aerobics dancing, cycling and other miscellaneous exercise (specified by each patient). The duration engaged in each activity in min/time was multiplied by that activity's typical energy expenditure, expressed in MET, based on the newest compendium of Ainsworth [23]; then overall activity was summed to yield a MET h score per week. The energy expended by sitting quietly, 1 MET, is equivalent to 3.5 ml oxygen uptake (kg body weight)$^{-1}$ min^{-1} or 4.184 kJ (1 kcal) (kg body weight)$^{-1}$ h^{-1}.

Other lifestyle variables A baseline dietary survey, which was validated and is widely used in Japan [24], was undertaken. This consisted of food records and a food frequency questionnaire, which included questions on alcohol consumption. Information on cigarette smoking was collected using a self-administered questionnaire. Smoking status was classified into one of three categories: current smokers, ex-smokers and never smokers [25]. Occupation was surveyed by a self-administered questionnaire based on the Japan Standard Classification of Occupations [26], which was also used in the National Health and Nutritional Examination Survey in Japan. Occupations were: (1) professional or skilled workers and technicians; (2) administrative or managerial; (3) office or clerical; (4) sales; (5) service; (6) armed force and police; (7) agricultural, forestry and fishery; (8) transport, trades and storage; (9) labourers in manufacturing, mining and construction and (10) no work or housewife. Occupations in categories 1, 2, 3 and 10 were classified as sedentary and the remainder were defined as physically active.

Clinical and laboratory measurements Patients were assessed yearly after the baseline evaluation. Mean values for at least two measurements each year were obtained for HbA_{1c}, fasting plasma glucose and fasting serum lipids. HbA_{1c} assays were performed according to procedures outlined by the Laboratory Test Committee of the JDS, which is known to be converted by the formula HbA_{1c} (JDS) (%)= $0.98 \times HbA_{1c}$ (National Glycohaemoglobin Standardisation Program; NGSP) (%)+0.25%. All other laboratory tests were done at each participating institute. Serum LDL-cholesterol was calculated using Friedewald's equation, except where triacylglycerols exceeded 4.52 mmol/l (400 mg/dl), in which case LDL-cholesterol data were treated as 'missing'. This was applicable to 19 participants. All other measurements, including those for body weight, blood pressure and a 12-lead ECG, were performed at least once yearly.

Outcome measures A fatal or first non-fatal manifestation of CHD (angina pectoris or myocardial infarction) was diagnosed according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO/MONICA) project. A patient with a first percutaneous coronary intervention or coronary artery bypass graft was also counted as having a CHD event. Information regarding primary outcome and other clinical variables for each individual was collected through an annual report that included detailed findings at the time of the event from each participating diabetologist who was providing care to those patients. Adjudication of endpoints was by central committees comprised of experts in diabetology as well as cardiology who were masked to risk factor status, including information on LTPA, and was based on additional data such as a detailed history, sequential changes in ECG and serum cardiac biomarkers and results of coronary angiography. Information regarding vital status and causes of death was also obtained through an annual report form and causes of death were classified based on the ninth revision of the International Classification of Diseases (ICD-9) Clinical Modification codes (www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm) for cardiovascular disease (diagnosis codes 390–452), cancer (diagnosis codes 140–208) and other miscellaneous causes.

Statistical analysis

All statistical analyses and data management were conducted at a central data centre. Patient characteristics were described as mean ± SD, median and interquartile range or percentage. HRs of the incidence of each outcome for higher tertiles of LTPA compared with the lowest tertile of LTPA

were estimated by Cox regression and also by competing risk regression, which accounts for the influence of non-cardiovascular mortality when analysing associations between LTPA and CHD or stroke. These models included as confounders age, sex, diabetes duration, smoking, energy/ethanol intake, occupation (physically active/sedentary), BMI, systolic blood pressure and levels of HbA_{1c}, LDL-cholesterol, HDL-cholesterol and triacylglycerols. The p value for trend was calculated using the same regression models except that the tertile was treated as a linear term. Survival curves for each outcome according to tertiles were estimated by the Kaplan–Meier method. All p values are two-sided and the significance level is 0.05. All statistical analyses were conducted using SAS ver. 9.2 (SAS Institute, Cary, NC, USA).

Results

During the median follow-up period of 8.05 years, the crude incidence rates per 1,000 patient-years of CHD, stroke and death were 9.56 (95% CI 7.95, 11.48; 114 events, 11,928 person-years), 7.40 (95% CI 6.01, 9.11; 89 events, 12,022 person-years) and 5.60 (95% CI 4.42, 7.09; 69 events, 12,314 person-years), respectively. The 8-year follow-up rate was 77%. Regarding causes of death, 36 deaths (52.2%) were from cancer, 16 (23.2%) from cardiovascular disease and sudden death, 12 (17.4%) due to other known causes and 5 (7.2%) due to undetermined causes. Table 1 summarises the baseline clinical characteristics of participants and the incidence of CHD, stroke and mortality according to tertiles of LTPA. The mean LTPA level of the individuals in the bottom tertile was less than 1 MET h/week and that for the middle tertile was nearly 10 MET h/week. Individuals in the top tertile had LTPA levels approximately four times higher than those in the middle tertile on average. Among these groups, the difference in age was only marginal, and there were no significant trends in sex, blood pressure, LDL-cholesterol, medication or energy intake. Significant negative trends across all groups in the degree of obesity and glycaemia and borderline significant trends in triacylglycerol levels were observed whereas there was a significant positive trend in the HDL-cholesterol level. Compared with individuals with a lower level of LTPA, those with higher LTPA included a significantly higher proportion of individuals with sedentary occupations, moderate ethanol intake and a lower smoking rate.

Table 2 shows HRs for CHD, stroke and total mortality according to tertiles of LTPA determined by Cox multivariate models adjusted as follows: by age, sex and diabetes duration (Model 1); Model 1 plus lifestyle factors (i.e. smoking, occupation and intakes of alcohol, energy, saturated fatty acids and dietary fibre [27]) (Model 2); Model 2 plus clinical variables (i.e. BMI, systolic blood pressure, HbA_{1c} and serum lipids) (Model 3); and Model 3 plus medications (agents for glycaemia, hypertension or dyslipidaemia) (Model 4). These adjustments were made to clarify whether lifestyle factors other than LTPA confounded the results or whether exercise exerted its effects via improvement of known cardiovascular risk factors. While there was a tendency toward a lower HR for CHD in association with an increase in LTPA, it was not statistically significant. In contrast, significant reductions in risks for stroke and total mortality were seen, and HRs for both stroke and total mortality in the top tertile were approximately half of those in the bottom tertile. The significance in total mortality was not affected by adjustment for lifestyle factors, clinical variables and medications (Table 2). Although stroke risk in the top tertile was significant after adjustment for age, sex and diabetes duration, HRs for the top tertile became of borderline significance (but still with a significant p value for trend, 0.0495) after adjustment for lifestyle factors; the p value was more than 0.1 after additional adjustment for clinical variables. On the other hand, analysis by a competing risk model that aimed to exclude the influence of mortality cases when assessing associations between LTPA and CHD or stroke did not fundamentally change the results (Table 2).

Probability in each outcome according to the tertile of LTPA determined by Kaplan–Meier analysis is shown in Fig. 1. A consistently lower risk of stroke and total mortality was found in the top tertile. Subgroup analysis (Fig. 2) revealed that among men or non-smokers the HR for stroke in individuals in the top tertile of LTPA was significantly lower than in those in the bottom tertile. Similarly, among those who were 60 years or older, were non-smokers, had a sedentary occupation, were not obese (BMI<25 kg/m^2), had hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg or those taking medication for hypertension) or who did not have dyslipidaemia (LDL-cholesterol <3.10 mmol/l [120 mg/dl], triacylglycerol <1.69 mmol/l [150 mg/dl], HDL-cholesterol ≥1.03 mmol/l [40 mg/dl] and those not taking medication for dyslipidaemia), the HR for total mortality was lower in the top tertile than in the bottom tertile of LTPA. However, there were no significant interactions among these factors, suggesting lack of clear evidence of heterogeneity regarding the effect of LTPA on outcomes (Fig. 2).

Discussion

In comparison with type 2 diabetic patients in Western countries, those in East Asian countries, including Japan, are known to have quite different features regarding cardiovascular complications and their risk factors [22, 28–30]. Diabetic individuals in East Asian countries have a much lower degree of obesity and a much lower incidence of CHD

Table 1 Baseline characteristics of the 1,702 Japanese patients with type 2 diabetes according to tertile of LTPA

Characteristic No. of patients	Total n=1702	Tertile 1 (≤3.7 MET h/week) n=551	Tertile 2 (3.8–15.3 MET h/week) n=589	Tertile 3 (≥15.4 MET h/week) n=562	p for trend
LTPA (MET h/week)	15.5±20.8	0.8±1.1	9.1±3.8	36.8±24.4	<0.01
Women (%)	47.1	48.3	48.4	44.5	0.20
Age (years)	58.5±6.9	57.9±7.2	58.7±6.8	59.0±6.7	0.01
Diabetes duration (years)	11.0±7.1	10.4±6.6	11.0±7.3	11.6±7.4	0.01
Sedentary occupation (%)	74.1	67.1	75.6	77.8	<0.01
BMI (kg/m^2)	23.0±3.0	23.2±3.2	23.0±3.0	22.7±2.9	0.01
Waist circumference (cm)	79.4±9.2	80.0±9.4	79.6±9.1	78.5±9.0	0.01
Systolic blood pressure (mmHg)	131.7±16.3	131.5±16.4	132.1±16.5	131.6±16.1	0.88
Diastolic blood pressure (mmHg)	76.7±9.9	76.8±10.0	76.8±10.0	76.6±9.9	0.71
HbA_{1c} (JDS) (%)	7.9±1.3	8.0±1.4	7.8±1.2	7.8±1.2	<0.01
HbA_{1c} (IFCC) (mmol/mol)	67.0±14.2	68.8±15.6	66.3±13.4	66.0±13.4	<0.01
Fasting plasma glucose (mmol/l)	8.85±2.41	9.10±2.59	8.71±2.18	8.77±2.45	0.03
LDL-cholesterol (mmol/l)	3.17±0.83	3.18±0.84	3.17±0.85	3.16±0.78	0.67
HDL-cholesterol (mmol/l)	1.42±0.44	1.37±0.42	1.41±0.42	1.48±0.45	<0.01
Triacylglycerols[a] (mmol/l)	1.15±0.80	1.21±0.80	1.18±0.84	1.08±0.72	0.05
Treated by insulin/OHA without insulin (%)	22.1/65.7	22.9/68.6	21.3/64.5	22.1/64.2	0.76/0.13
Use of agents for hypertension (%)	25.9	30.7	24.6	22.4	<0.01
Use of agents for dyslipidaemia (%)	24.0	24.9	23.6	23.4	0.55
Current smoker (%)	27.6	31.0	30.2	22.1	<0.01
Energy intake (kJ/day)	7,183±1,469	7,145±1,540	7,217±1,473	7,175±1,415	0.82
Saturated fatty acid intake (g)	15.4±5.1	15.4±5.4	15.5±5.1	15.2±4.9	0.73
Dietary fibre intake (g)	14.6±5.2	14.0±5.4	14.7±5.2	15.1±5.1	<0.01
Ethanol intake (per day): never, 3 drinks or less, more than 3 drinks (%)[b]	62.1/31.5/6.4	66.5/26.9/6.6	61.9/31.7/6.3	57.9/35.8/6.3	<0.01/<0.01/0.83
No. of outcome incidents					
CHD	114	38	42	34	-
Stroke	89	33	33	23	-
Mortality	69	26	27	16	-

Data are means (±SD for continuous variables)

[a] Median (interquartile range)

[b] 'One drink' is equivalent to 12.6 g of ethanol based on the US Department of Agriculture definition

OHA, oral hypoglycaemic agent

than those in Western countries [28, 31]. Furthermore, cardiovascular disease is not necessarily a leading cause of death among diabetic patients in Japan [32], which is in distinct contrast to Western patients with diabetes [1]. Despite these differences, only two studies have prospectively investigated associations between physical activity and mortality and morbidity in Asian populations with diabetes [4, 7]. This is notable, as Asian diabetic patients account for more than 60% of the world's diabetes population [28]. One was a recent report from Taiwan [7] that used a self-reported bivariate response of whether exercise was performed regularly as the only physical activity variable. The other study was from Japan [4] and involved only individuals with diabetes who were more than 65 years of age and demonstrated dose-dependent effects of physical activity that were evaluated and scored, although not by the use of universal MET h units. Therefore, information on the recommended level of physical activity required to prevent complications in Asian patients with diabetes is scarce.

The current results for Japanese individuals with type 2 diabetes revealed that 15.4 MET h/week or more of LTPA was associated with a significant reduction in risk of stroke and total deaths (by approximately half) compared with 3.7 MET h/weekor less of LTPA. The cut-off of 15.4 MET h/week in the current analysis corresponds to 2.2 MET h/day which is, for example, equivalent to 30 min/day of brisk walking (3.5 miles [5.6 km]/h) and is 4.3 MET [23]. This is

Table 2 HRs with 95% CIs for LTPA according to tertiles (HRs for lowest tertile [≤3.7 MET h/week] as a reference) for cardiovascular disease (CHD and stroke) or total mortality risk analysed by Cox regression or competing risk regression

Analysis	Cox regression					Competing risk regression adjusted for non-cardiovascular death				
	Tertile 2 (LTPA 3.8–15.3 MET h/week) (vs Tertile 1 [LTPA ≤3.7 MET h/week])		Tertile 3 (LTPA ≥15.4 MET h/week) (vs Tertile 1 [LTPA ≤3.7 MET h/week])		*p* for trend	Tertile 2 (LTPA 3.8–15.3 MET h/week) (vs Tertile 1 [LTPA ≤3.7 MET h/week])		Tertile 3 (LTPA ≥15.4 MET h/week) (vs Tertile 1 [LTPA ≤3.7 MET h/week])		*p* for trend
	HR (95% CI)	*p*	HR (95% CI)	*p*		HR (95% CI)	*p*	HR (95% CI)	*p*	
CHD										
Model 1[a]	0.98 (0.63, 1.52)	0.92	0.77 (0.48, 1.25)	0.29	0.29	0.98 (0.63, 1.53)	0.92	0.80 (0.50, 1.29)	0.36	0.35
Model 2[b]	0.97 (0.57, 1.65)	0.91	0.71 (0.40, 1.24)	0.23	0.19	0.95 (0.55, 1.67)	0.87	0.73 (0.41, 1.32)	0.30	0.26
Model 3[c]	1.00 (0.58, 1.71)	0.99	0.77 (0.43, 1.37)	0.37	0.34	0.99 (0.57, 1.75)	0.98	0.78 (0.42, 1.43)	0.42	0.37
Model 4[d]	0.96 (0.56, 1.65)	0.87	0.77 (0.43, 1.38)	0.38	0.35	0.96 (0.53, 1.71)	0.88	0.78 (0.42, 1.43)	0.42	0.39
Stroke										
Model 1	0.78 (0.48, 1.27)	0.32	0.55 (0.32, 0.94)	0.03	0.03	0.78 (0.48, 1.28)	0.33	0.55 (0.33, 0.94)	0.03	0.03
Model 2	1.08 (0.58, 2.01)	0.80	0.49 (0.23, 1.03)	0.06	0.0495	1.09 (0.58, 2.03)	0.79	0.49 (0.23, 1.07)	0.07	0.04
Model 3	1.23 (0.65, 2.34)	0.53	0.56 (0.26, 1.20)	0.13	0.10	1.24 (0.65, 2.36)	0.51	0.56 (0.25, 1.26)	0.16	0.10
Model 4	1.27 (0.67, 2.43)	0.47	0.57 (0.26, 1.23)	0.15	0.12	1.28 (0.67, 2.44)	0.46	0.57 (0.25, 1.30)	0.18	0.12
CHD or stroke										
Model 1	0.89 (0.61, 1.28)	0.52	0.71 (0.48, 1.05)	0.09	0.09	0.89 (0.61, 1.28)	0.52	0.73 (0.50, 1.08)	0.11	0.11
Model 2	0.94 (0.60, 1.46)	0.77	0.61 (0.38, 0.99)	0.04	0.03	0.93 (0.59, 1.46)	0.75	0.64 (0.39, 1.04)	0.07	0.052
Model 3	0.96 (0.62, 1.50)	0.86	0.67 (0.41, 1.09)	0.10	0.09	0.96 (0.61, 1.51)	0.86	0.67 (0.41, 1.11)	0.12	0.09
Model 4	0.96 (0.61, 1.50)	0.85	0.68 (0.42, 1.11)	0.12	0.10	0.96 (0.61, 1.51)	0.85	0.68 (0.41, 1.13)	0.14	0.11
Total mortality										
Model 1	0.80 (0.46, 1.38)	0.42	0.49 (0.26, 0.91)	0.02	0.02	-	-	-	-	-
Model 2	0.80 (0.43, 1.49)	0.49	0.41 (0.20, 0.87)	0.02	0.02	-	-	-	-	-
Model 3	0.85 (0.46, 1.59)	0.62	0.46 (0.22, 0.98)	0.04	0.04					
Model 4	0.88 (0.47, 1.64)	0.68	0.47 (0.22, 0.99)	0.047	0.046	-	-	-	-	-

[a] Model 1, adjusted by age, sex, diabetes duration

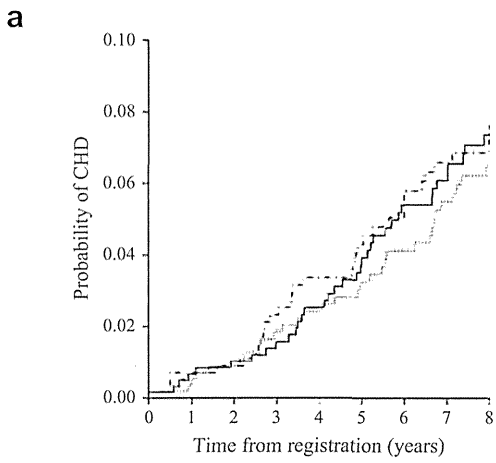
[b] Model 2, model 1 plus lifestyle factors (smoking, energy/ethanol intake, dietary fibre, saturated fatty acid and type of occupation)

[c] Model 3, model 2 plus clinical variables (BMI, HbA_{1c}, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triacylglycerols)

[d] Model 4, model 3 plus treatment with insulin, oral hypoglycaemic agents, antihypertensive agents or lipid-lowering agents

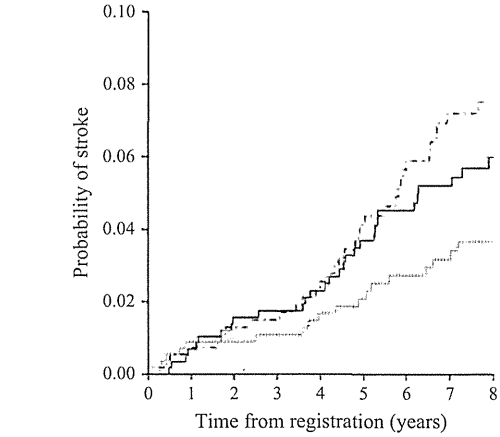
also relatively close to, but somewhat more than, the amount recommended by the Joint Position Statement of the American Diabetes Association/American College of Sports Medicine [2] and the Scientific Statement of the American Heart Association [3], both of which recommend 150 min/week of exercise of moderate or greater intensity. According to previous studies using almost identical quantitative methods for men [18] and women [21] in the USA, significantly reduced multivariate-adjusted risk (approximate HR 0.6) for total cardiovascular disease or total mortality was observed from approximately 12–16 MET h/week, which is close to our cut-off.

A characteristic finding of the current analysis was that among cardiovascular events stroke and not CHD was significantly reduced by LTPA, a result different from that found in diabetic women in the USA [21]. Interestingly, however, even in those results [21], a significantly reduced incidence of ischaemic stroke was seen beginning with fewer mean hours of moderate-to-vigorous activity per week (i.e. 2–3.9 h/week) compared with the significant reduction in CHD that was observed starting with 4–6.9 h/week. This suggests that exercise could be more effective in preventing stroke than CHD. Significantly decreased mortality risks from cerebrovascular or non-CHD cardiovascular disease, but not heart disease or CHD, by exercise were also reported in other individuals with diabetes in the USA [19] as well as in Japanese women in the general population [33]. While this manuscript was in preparation, analysis of another Japanese diabetic cohort that included only individuals over the age of 65 years demonstrated that physical activity as



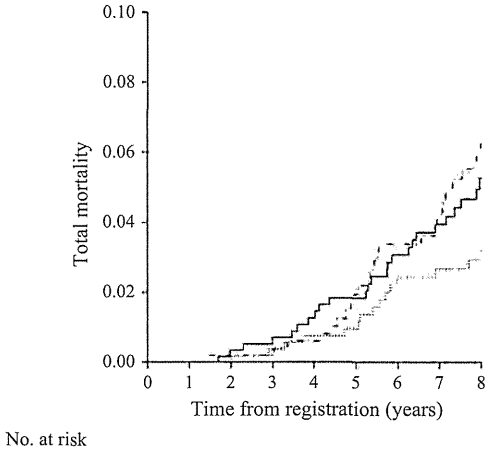
No. at risk

T1 of LTPA	551	542	508	473	443	391	375	344	235
T2 of LTPA	589	580	559	533	503	465	430	391	283
T3 of LTPA	562	556	535	511	491	455	427	403	289



No. at risk

T1 of LTPA	551	542	506	478	451	392	375	343	237
T2 of LTPA	589	581	557	532	504	469	438	397	286
T3 of LTPA	562	555	536	516	497	464	435	414	301



No. at risk

T1 of LTPA	551	546	515	486	464	410	391	367	248
T2 of LTPA	589	584	567	545	521	489	457	418	302
T3 of LTPA	562	558	542	523	504	478	448	427	312

◀ **Fig. 1** Probability of coronary heart disease (**a**), stroke (**b**) or total mortality (**c**) according to tertiles of LTPA determined by the Kaplan–Meier method. Broken line, tertile 1 (T1) of LTPA (≤3.7 MET h/week); solid line, tertile 2 (T2) of LTPA (3.8–15.3 MET h/week); dotted line, tertile 3 (T3) of LTPA (≥15.4 MET h/week)

evaluated and scored was significantly associated only with cerebrovascular events and not with cardiac events [4].

The precise mechanisms for these findings cannot be clarified merely from epidemiological studies. Although statistically nonsignificant, since a weak tendency for a decrease in HR for CHD across LTPA tertiles was observed in our cohort, it is possible that the relationship between CHD and LTPA would become significant with a longer period of observation. Because the biological mechanisms for stroke prevention by physical activity in patients with type 2 diabetes are only partially understood [34], the possibility exists that exercise ameliorates undetermined cardiovascular risk factors, such as quality of life [2] or other health behaviours [3], which more strongly affect stroke risk than CHD risk. This possibility should be investigated in the future.

The significant risk reduction in stroke by LTPA was weakened after stepwise adjustment for lifestyle factors and clinical variables, which suggested that some of the involved elements confounded the association although these adjustments did not compromise the beneficial effects of LTPA. However, these findings could be helpful in understanding the mechanisms behind the associations. Individual adjustments for each lifestyle factor instead of simultaneous adjustment for all lifestyle factors suggested that dietary factors (intake of energy, saturated fat and dietary fibre) had a relatively larger effect than the other lifestyle factors, suggesting that individuals who exercised more also had a tendency to pay more attention to the amount and content of meals (see ESM Table 1). On the other hand, individual adjustments for each clinical variable instead of simultaneous adjustment for all clinical variables suggested that triacylglycerol and LDL-cholesterol had a larger effect than the other clinical variables, indicating that LTPA might have exerted its effect on stroke reduction partly through ameliorating serum lipids (see ESM Table 1). Even though it became nonsignificant, the fully adjusted HR and its p value for stroke did not alter dramatically from those when adjusted only by age, sex and diabetes duration. This suggests that undetermined risk factors associated with physical activity should exist. This is also supported in part by the results of subgroup analysis of the risk of stroke and total mortality, which indicated that greater LTPA was not necessarily associated with lower risk in those who had typical cardiovascular risk factors.

The current results suggested that the effect of exercise on total mortality was independent of lifestyle factors and clinical variables, which included typical cardiovascular risk

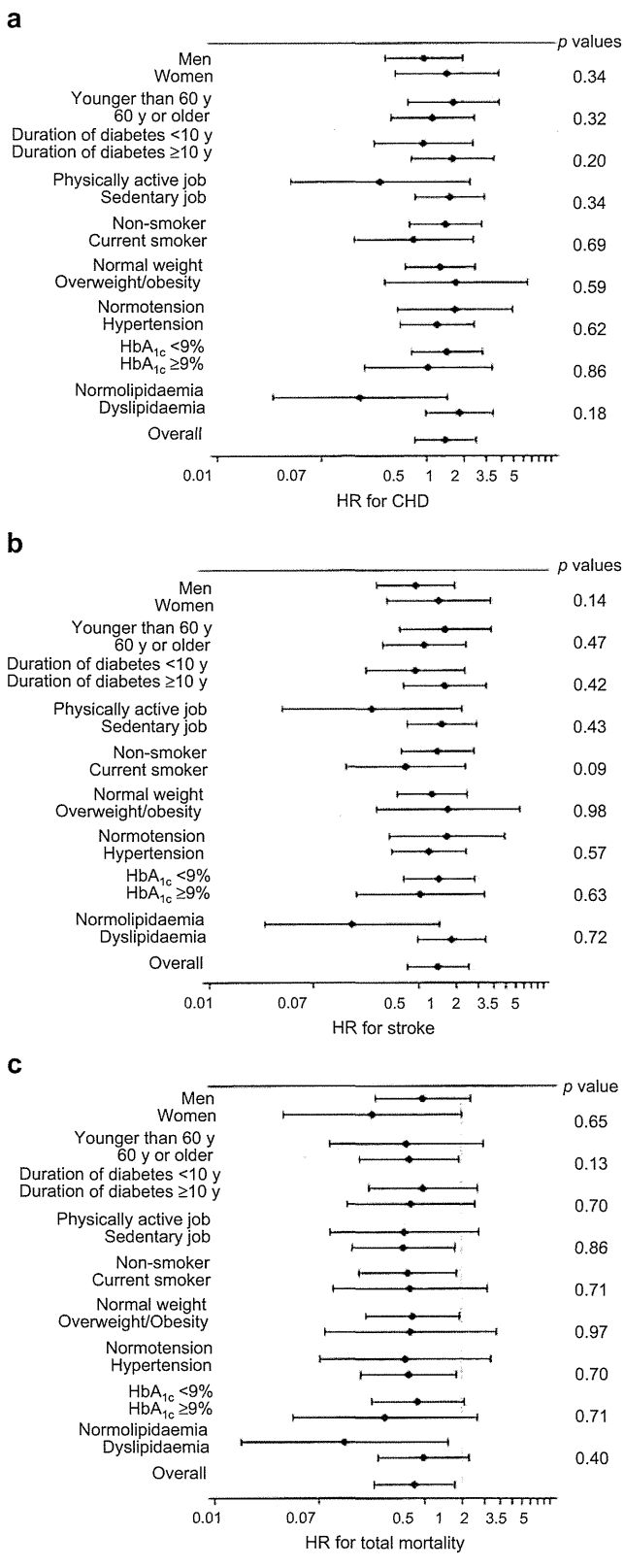


Fig. 2 Subgroup analysis adjusted for age, sex, duration of diabetes and lifestyle factors. HRs for CHD (**a**), stroke (**b**) and total mortality (**c**) are shown for tertile 3 vs tertile 1 (reference) for LTPA. Bars in the figure indicate 95% CIs. Normal weight is defined as BMI <25 kg/m^2; normotension is defined as systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg and not under medication for hypertension; and normolipidaemia is defined as serum levels of LDL-cholesterol <3.10 mmol/l (120 mg/dl), triacylglycerols <1.69 mmol/l (150 mg/dl), HDL-cholesterol >1.03 mmol/l (40 mg/dl) and not under medication for dyslipidaemia. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

factors such as smoking, dyslipidaemia and hypertension. Since it is well known that the majority of Western individuals with diabetes die from cardiovascular diseases and that exercise is known to improve cardiovascular risk factors [1], it is natural to consider that physical activity ameliorates mortality mainly through preventing cardiovascular events [2, 3]. In this study, we unfortunately could not evaluate the effect of CHD and stroke on total mortality since a cause-specific mortality could not be calculated because of the limited number of events. Although difficult to prove, the current findings suggest that the significant reduction in mortality related to LTPA was not derived from a reduction in CHD and stroke but from a reduction in causes of death other than CHD or stroke. Cancer was the top cause of death among our study participants, which is in accordance with previously reported results in the diabetic [32] as well as the general [33] population in Japan. This might suggest that an enhanced risk of cancer by diabetes [35] could be somewhat counterbalanced by the effect of exercise. There is strong and consistent evidence that physical activity reduces the risk of cancer [33, 35, 36], including that in the general Japanese population [33]. The amount of physical activity recommended for cancer prevention (i.e. 30–60 min of moderate- or vigorous-intensity exercise at least 5 days per week) [36] is close to that recommended for diabetic persons [2, 3].

Our study has several strengths. It was a large-scale study with nationwide sampling from nearly 60 institutes, LTPA was quantified using a universal MET score, and dietary data were available. The results were also confirmed by competing risk models as well as detailed adjustment models to clarify the underlying mechanisms. Nevertheless, some limitations of this investigation deserve consideration. One is the observational design, which could allow the possibility of unmeasured confounders. The limited number of participants prevented us from analysing data separately by sex or by quartiles or quintiles instead of tertiles. The necessity of a large-scale cohort study in the future is implied by our results. All of our participants were recruited from clinics of universities or large general hospitals, which might limit the extrapolation of the results to primary care settings. However, they were not necessarily tertiary-care patients since the health insurance system in Japan allows patients to freely choose outpatient clinics regardless of severity or degree of progression of diabetes. We could not

determine physical activity related to occupation and commuting since we did not survey working hours per week or commuting methods. However, Hu and colleagues [37] reported that physical activity related to occupation and commuting significantly affected the results in their cohort of individuals with diabetes [10], although adjustment by individual or dichotomous (physically active/sedentary) classifications of occupations did not affect our results. It might be meaningful to show the effects of LTPA independently of occupation since an occupation per se is not an easily 'modifiable' element for many individuals. Only baseline data, including those using medication, were considered in this analysis; however, adjustment by baseline use of medication did not fundamentally change our results, therapeutic management during the follow-up period could have influenced these results. In fact, we found a substantial increase in usage of antihypertensive and hypolipidaemic agents during the follow-up period, as previously reported [38]. However, it would not be appropriate to adjust for the influence of medications during follow-up in our analysis, as these variables can be outcomes of low LTPA at baseline. We could only show that clinical variables according to tertiles of LTPA remained quite stable during the observational period (see ESM Fig. 1).

Loss to follow-up is an inevitable problem in most cohort studies. In this study, the 8-year follow-up rate was not necessarily high, and LTPA, total energy intake and treatment with insulin were associated with follow-up status (see ESM Table 2). Theoretically, in such cases, a valid analysis requires inclusion of all observed prognostic factors associated with follow-up status into the model, even under the assumption of 'missing at random'. Taken together, HRs should be estimated with adjustment for LTPA, total energy intake and treatment by insulin, and Model 4 in Table 2 is the least likely to be biased according to this theoretical consideration. We did not assess cardiorespiratory fitness, which is known to be closely related to cardiovascular events in general [39] and in diabetic populations [40, 41], although the beneficial effects of LTPA are not fully explained only by cardiorespiratory fitness [42, 43].

In conclusion, in our cohort of Japanese individuals with type 2 diabetes, an LTPA level of 15.4 MET h/week of more was associated with a significantly lower risk of stroke through, at least partially, ameliorating the effects of combinations of known cardiovascular risk factors. Higher LTPA was also associated with significantly reduced total mortality but independent of cardiovascular risk factors or events. These findings, which imply differences from Western diabetic populations, should be considered in the clinical management of East Asians with diabetes.

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Contribution statement All authors contributed to the conception and design of the study, acquisition, analysis and interpretation of data and drafting and editing the manuscript. All of the authors approved the final version of the manuscript. H. Sone 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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Diabetic Retinopathy and Microalbuminuria Can Predict Macroalbuminuria and Renal Function Decline in Japanese Type 2 Diabetic Patients

Japan Diabetes Complications Study

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OBJECTIVE—To examine the interactive relationship between diabetic retinopathy (DR) and diabetic nephropathy (DN) in type 2 diabetic patients, and to elucidate the role of DR and microalbuminuria on the onset of macroalbuminuria and renal function decline.

RESEARCH DESIGN AND METHODS—We explored the effects of DR and microalbuminuria on the progression of DN from normoalbuminuria and low microalbuminuria (<150 mg/gCr) to macroalbuminuria or renal function decline in the Japan Diabetes Complications Study (JDCS), which is a nationwide randomized controlled study of type 2 diabetic patients focusing on lifestyle modification. Patients were divided into four groups according to presence or absence of DR and MA: normoalbuminuria without DR [NA(DR−)] (n = 773), normoalbuminuria with DR [NA(DR+)] (n = 279), microalbuminuria without DR [MA(DR−)] (n = 277), and microalbuminuria with DR [MA(DR+)] (n = 146). Basal urinary albumin-to-creatinine ratio and DR status were determined at baseline and followed for a median of 8.0 years.

RESULTS—Annual incidence rates of macroalbuminuria were 1.6/1,000 person-years (9 incidences), 3.9/1,000 person-years (8 incidences), 18.4/1,000 person-years (34 incidences), and 22.1/1,000 person-years (22 incidences) in the four groups, respectively. Multivariate-adjusted hazard ratios of the progression to macroalbuminuria were 2.48 (95% CI 0.94–6.50; P = 0.07), 10.40 (4.91–22.03; $P < 0.01$), and 11.55 (5.24–25.45; $P < 0.01$) in NA(DR+), MA(DR−), and MA(DR+), respectively, in comparison with NA(DR−). Decline in estimated glomerular filtration rate (GFR) per year was two to three times faster in MA(DR+) (−1.92 mL/min/1.73 m^2/year) than in the other groups.

CONCLUSIONS—In normo- and low microalbuminuric Japanese type 2 diabetic patients, presence of microalbuminuria at baseline was associated with higher risk of macroalbuminuria in 8 years. Patients with microalbuminuria and DR showed the fastest GFR decline. Albuminuria and DR should be considered as risk factors of renal prognosis in type 2 diabetic patients. An open sharing of information will benefit both ophthalmologists and diabetologists.

Diabetic retinopathy (DR) and nephropathy (DN) are two major chronic microvascular complications in long-standing type 1 and type 2 diabetic patients. However, it is still unclear whether these 2 complications are related to or affect each other or whether both of them progress simultaneously after their onset, although many epidemiological studies have shown the coexistence of DR and DN (1,2). In fact, we sometimes see proteinuric diabetic patients without DR or normoalbuminuric patients with proliferative DR, which is the most advanced stage of DR. For example, it was shown that only 36% had no DR, while 53% had nonproliferative, 9% moderate to severe, and 2% severe DR in 285 normoalbuminuric Caucasian type 1 diabetic patients (3). In addition, there was marked discordance between DR and DN, especially in normoalbuminuria or low-level microalbuminuria, while advanced renal histological severity has been related to advanced DR severity in Caucasian type 1 diabetic patients (4). On the other hand, diabetic patients treated by diabetologists sometime miss their visits to ophthalmologists; therefore, the relationships or detailed clinical courses of DR and DN can hardly be analyzed in most clinical sites.

All over the world, DN is a major cause of end-stage renal disease, which

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requires renal replacement therapy such as hemodialysis or renal transplantation (5,6). In Japan, the number of patients requiring renal replacement therapy has increased threefold in the last 15 years. Therefore, it is absolutely necessary to stop the progression of DN and to find biomarkers or easily available factors that represent the exact clinical course or prognosis of DN. However, it is not exactly known what factors affect an increase of urinary albumin excretion (UAE) or glomerular filtration rate (GFR) decline, which are typical clinical changes in DN.

Microalbuminuria is well-known as a risk factor resulting in macroalbuminuria in type 1 and type 2 diabetic patients (7–9). In addition, some Caucasian type 2 diabetic patients with microalbuminuria showed rapid decline of GFR, although it was unclear whether these patients had more frequent DR compared with the patients without rapid GFR decline (10). On the other hand, DR was shown to be a risk factor of microalbuminuria and macroalbuminuria (2,11). In addition, proliferative DR was shown to be a predictor of macroalbuminuria in Caucasian type 1 diabetic patients (13), but this association has not been investigated in Asian populations. Although DR and glomerulosclerosis seemed to be parallel to progress using the investigation of serial renal biopsy specimens (14) when the blood glucose control was fair to poor, detailed interaction between two complications are still obscure in a large number of patients. Whether DR can predict renal functional decline in type 1 and type 2 diabetic patients remains to be clarified.

The Japan Diabetes Complications Study (JDCS) is a nationwide randomized controlled study of type 2 diabetic patients focusing on lifestyle modification (15,16). We have reported the extremely low transition rate from normoalbuminuria and low microalbuminuria in this Japanese cohort (9), as well as incidence and progression rates of DR that were also lower than in Caucasian populations (15). In addition, we have also shown that the incidence and progression rate of DR were lower than those in Caucasian populations and that glycemic control, duration of diabetes, and systolic blood pressure (SBP) were related to DR in the JDCS cohort (17). Here, we elucidated the relationships between DN and DR, and the risk factors of the UAE increase and GFR decline according to the presence or absence of microalbuminuria or DR in the JDCS cohort.

RESEARCH DESIGN AND METHODS

—This study is a part of the JDCS, a Japanese nationwide multicentered randomized trial (15). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1C} levels of >6.5% were recruited and registered from 59 hospitals specializing in diabetes care. 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 ethics approval from the institutional review boards of all the participating institutes. Written informed consent was obtained from all patients enrolled. The inclusion criteria for participating patients have previously been described (15). Those who had impaired glucose tolerance and major ocular disease including glaucoma, dense cataract, or history of cataract surgery were excluded. A final total of 2,033 patients aged 58.5 ± 6.9 (mean ± SD) years were included in the study, and their known diabetes duration was 10.9 ± 7.2 years.

The protocol originally specified that patients with nondiabetic nephropathy, macroalbuminuria, serum creatinine levels >120 μmol/L, and mean values of two spot urine examinations for an albumin excretion rate of >150 mg/g creatinine were excluded in the analysis of nephropathy, making up the analysis population of 1,558 patients (9). We excluded the patients with high microalbuminuria (150–300 mg/gCr) because the INNOVATION (Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 diabetic Nephropathy) trial showed a higher transition rate from high microalbuminuria to macroalbuminuria (18). After exclusion of 83 patients without DR assessment, the remaining 1,475 patients were divided into four groups according to the absence or presence of DR and microalbuminuria as follows: normoalbuminuria without DR [NA(DR−)] (n = 773), normoalbuminuria with DR [NA(DR+)] (n = 279), microalbuminuria without DR [MA(DR−)] (n = 277), and microalbuminuria with DR [MA(DR+)] (n = 146).

Assessment of DR

The presence and severity of DR were determined annually by qualified ophthalmologists at each institute by mydriatic indirect ophthalmoscopic examination and slit lamp biomicroscopic fundus examination using precorneal lens with the international DR and diabetic macular edema disease scales including minor modifications (17,19). To validate the consistency of staging between study sites, we cross-examined fundus images and evaluated the agreement in staging between local ophthalmologists and retinal specialists (17). Severity of DR was categorized following the international clinical diabetic retinopathy severity scales into five categories as "no retinopathy" (equivalent to the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale level 10), "mild nonproliferative DR" (stage 1; equivalent to ETDRS level 20), "moderate nonproliferative DR" (stage 2; equivalent to ETDRS levels 35, 43, and 47), "severe nonproliferative DR" (stage 3; equivalent to ETDRS levels 53A–53E), and "proliferative DR" (stage 4; equivalent to ETDRS levels ≥61) (19). History of ocular surgery (e.g., cataract, glaucoma, and vitreoretinal surgery) was also surveyed.

Measures of kidney function

We followed up these groups for 8 years and measured their body weight and blood pressure at least twice a year. HbA_{1c}, fasting plasma glucose, serum lipids, and serum creatinine levels were also determined twice a year. Spot urinary albumin-to-creatinine ratio (UACR) was also determined at least twice a year using the turbidmetric immunoassay to measure the urinary albumin concentration. We defined normoalbuminuria as a UACR <30 mg/gCr and low microalbuminuria as a UACR of 30–150 mg/gCr. Estimated GFR (eGFR) was calculated using serum creatinine levels and ages according to the Modification of Diet in Renal Disease formula modified for the Japanese population (20).

Statistical analysis

The annual increase rate of UACR and decline rate of eGFR in each group was determined by linear mixed models. The transition from normo- or low microalbuminuria to macroalbuminuria (≥300 mg/gCr) was determined in two consecutive urine samples. Transition to macroalbuminuria was summarized by the annual transition rate to macroalbuminuria, and the remission proportion was defined by patients whose mean value of UACR at the final two visits was <30 mg/gCr. Hazard ratios of the NA(DR+), MA(DR−), and MA(DR+) groups compared with the NA(DR−) group as a reference adjusted for age, sex, HbA_{1c}, known duration of diabetes, SBP, and current smoking were estimated by Cox regression. All

P values are two sided, and the significance level is 0.05. All statistical analyses and data management were conducted at a central data center using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline clinical characteristics between four diabetic groups

LDL cholesterol, eGFR, and treatment of dyslipidemia did not differ between the four groups. Age, sex, HbA_{1c}, known duration of diabetes, BMI, blood pressure, HDL cholesterol, triglyceride, percent of current smokers, or treatment of diabetes and hypertension were different among the four groups at the baseline. UACR did not show any difference between NA(DR−) and NA(DR+) at normoalbuminuric levels or between MA(DR−) and MA(DR+) at microalbuminuric levels. The majority of the DR-positive patients had mild nonproliferative DR (stage 1) (Table 1).

Cox regression analysis for baseline albuminuria/retinopathy and incidence of macroalbuminuria

During the follow-up of a median of 8.0 years, a total of 73 progressions to macroalbuminuria were observed. The follow-up rate at 8 years was 78%. The numbers of death were 58 (3.9%) during the observation. Annual incidence rates of macroalbuminuria were 1.6/1,000 person-years (9 incidences), 3.9/1,000 person-years (8 incidences), 18.4/1,000 person-years (34 incidences), and 22.1/1,000 person-years (22 incidences) in the NA(DR−), NA(DR+), MA(DR−), and MA(DR+) groups, respectively. Table 2 shows multivariate-adjusted hazard ratios for the progression to macroalbuminuria. As shown, the hazard ratio of NA(DR+) compared with NA(DR−) was 2.48 (95% CI 0.94–6.50, $P = 0.07$). However, hazard ratios in MA(DR−) and MA(DR+) were 10.40 (4.91–22.03, $P < 0.01$), 11.55 (5.24–25.45, $P < 0.01$), and significantly higher than NA(DR−). These results also indicate that the hazard ratio for the direct comparisons between MA(DR+) and MA (DR−) is 0.90 (0.51–1.56, $P = 0.72$). Further, quantitatively similar trends are observed across severity of DR and microalbuminuria; hazard ratios of normoalbuminuria with stage 1, normoalbuminuria with stage 2–4, MA(DR−), microalbuminuria with stage 1 and microalbuminuria with stage 2–4 compared with NA(DR−) were 2.56 (0.95–6.90, $P = 0.06$), 2.38 (0.30–18.85, $P = 0.41$), 10.41 (4.92–22.01, $P < 0.01$), 10.06 (4.36–23.21, $P < 0.01$), and 21.30 (7.84–57.87, $P < 0.01$), respectively, using the same adjustment variables.

Clinical course of urinary albumin and eGFR among four groups >8 years old

Figure 1*A* and ***B*** show the UACR and eGFR over 8 years. The UACR had a trend toward an increase over time, and eGFR were decreased over time in all four groups. Annual increase rates of UACR in NA (DR+), MA(DR−) and MA(DR+) were 6.76 mg/gCr/year (95% CI 4.53–8.99, $P < 0.01$), 16.35 mg/gCr/year (13.97–18.74, $P < 0.01$), and 25.27 mg/gCr/year (22.13–28.41, $P < 0.01$), respectively, and they were significantly higher than in NA (DR−), which was 3.05 mg/gCr/year (1.72–4.39, $P < 0.01$). GFR decline per year in MA(DR+) was −1.92 mL/min/1.73 m^2/year (−2.28 to −1.55, $P < 0.01$) and was significantly faster than in NA (DR−), NA(DR+), and MA(DR−), which were −0.54 mL/min/1.73 m^2/year (−0.70 to −0.39, $P < 0.01$), −0.69 mL/min/1.73 m^2/year (−0.96 to −0.42, $P < 0.01$), and

Table 1—*Baseline characteristics of the 1,475 type 2 diabetic patients*

	NA(DR−)	NA(DR+)	MA(DR−)	MA(DR+)	ANOVA *P*
N	773	279	277	146	
Age (years)	57.9 ± 6.9	58.6 ± 6.9	59.2 ± 7.0	59.4 ± 6.5	<0.01
Mild nonproliferative DR (%)	0 (0)	239 (85.7)	0 (0)	117 (80.1)	ND
Moderate nonproliferative DR (%)	0 (0)	28 (10.0)	0 (0)	16 (11.0)	
Severe nonproliferative DR (%)	0 (0)	4 (1.4)	0 (0)	4 (2.7)	
Proliferative DR (%)	0 (0)	8 (2.9)	0 (0)	9 (6.2)	
Women, *n* (%)	348 (45.0)	149 (53.4)	134 (48.4)	69 (47.3)	<0.01
HbA_{1c} (%) (mmol/mol)	8.1 ± 1.3 (66 ± 14)	8.3 ± 1.2 (67 ± 13)	8.3 ± 1.3 (68 ± 15)	8.7 ± 1.4 (71 ± 15)	<0.01
Known diabetes duration (years)	9.7 ± 7.0	13.1 ± 7.4	9.5 ± 6.5	12.6 ± 6.3	<0.01
BMI (kg/m^2)	22.9 ± 3.0	22.6 ± 2.5	23.6 ± 3.1	23.9 ± 2.9	<0.01
SBP (mmHg)	129.3 ± 15.5	132.2 ± 15.6	136.5 ± 16.9	136.4 ± 16.9	<0.01
Diastolic BP (mmHg)	76.4 ± 9.9	75.9 ± 9.8	79.7 ± 10.0	77.5 ± 9.5	<0.01
LDL cholesterol (mg/dL)	122.2 ± 32.4	119.9 ± 31.7	125.8 ± 31.8	119.3 ± 33.9	0.12
HDL cholesterol (mg/dL)	54.4 ± 16.6	58.0 ± 18.0	53.1 ± 15.9	52.8 ± 14.3	<0.01
Triglyceride (mg/dL)	101.5 (74.0)	90.5 (60.0)	107.5 (85.0)	104.0 (78.0)	<0.01
Spot UACR (mg/gCr)	11.2 (0.05–30.0)	11.5 (0.01–29.9)	52.3 (30.0–148.9)	55.6 (30.0–147.4)	ND
eGFR (mL/min/1.73 m^2)	87.3 ± 28.7	86.0 ± 25.2	89.9 ± 33.5	87.5 ± 29.7	0.45
Treated by insulin (%)	108 (14.0)	87 (31.2)	33 (11.9)	38 (26.0)	<0.01
Treated by OHA without insulin (%)	504 (65.2)	195 (69.9)	170 (61.4)	107 (73.3)	0.04
Current smoker (%)	213 (27.6)	57 (20.4)	82 (29.6)	28 (19.2)	0.01
Treated by antihypertension agents	161 (20.8)	73 (26.2)	103 (37.2)	54 (37.0)	<0.01
Treated by lipid-lowering agents	179 (23.2)	76 (27.2)	71 (25.6)	37 (25.3)	0.55

Data are *n* (%), *n*, or means ± SD unless otherwise indicated. Triglyceride is expressed as median (interquartile range). UACR is expressed as median (range). ND, not done for the selection criteria; OHA, oral hypoglycemic agents.

Table 2—*Cox regression analysis for the incidence of macroalbuminuria by presence or absence of baseline albuminuria/retinopathy and other risk characteristics*

	Hazard ratio	95% CI	*P*
Normoalbuminuria			
Retinopathy absent	1	Ref.	—
Retinopathy present	2.48	(0.94–6.50)	0.07
Microalbuminuria			
Retinopathy absent	10.40	(4.91–22.03)	<0.01
Retinopathy present	11.55	(5.24–25.45)	<0.01
Age, +10 years	1.13	(0.78–1.61)	0.52
Sex, male/female	0.80	(0.46–1.38)	0.42
Known duration of diabetes, +10 years	1.10	(0.76–1.60)	0.61
HbA_{1c}, +1%	1.34	(1.15–1.56)	<0.01
SBP, +10 mmHg	1.10	(0.96–1.27)	0.17
Smoking status			
Past or never smoker	1	(Ref.)	—
Current smoker	1.90	(1.12–3.25)	0.02

−0.69 mL/min/1.73 m^2/year (−0.96 to −0.42, $P < 0.01$), respectively.

Course of UAE according to baseline diabetic retinopathy

As we found in the multivariate analysis in Table 2, patients with DR progressed from normoalbuminuria to high microalbuminuria (UACR; 150–300 mg/gCr) or macroalbuminuria (UACR >300 mg/gCr) more frequently than those without DR. However, remission rates of MA (DR−) and MA(DR+) groups from low microalbuminuria (UACR; 30 to 150 mg/gCr) at baseline to normoalbuminuria at the 8-year follow-up were 32.1 and 25.3%, respectively, showing no significant difference ($P = 0.18$) (Table 3).

CONCLUSIONS—In the previous report about DN in JDCS (9), we showed that the progression rate to macroalbuminuria from normoalbuminuria and low microalbuminuria was very low, and remission, i.e., normalization of low microalbuminuria to normoalbuminuria, was observed in 30.3% of patients. In the current study, we have shown that progression to macroalbuminuria was 2.48, 10.40, and 11.55 times faster than DR-free normoalbuminuria if patients had NA(DR+), MA(DR−), or MA(DR+), respectively. Of interest is the observation that the presence of both DR and microalbuminuria might be an important predictor of GFR decline in normoalbuminuric and low microalbuminuric type 2 diabetic patients during 8 years of follow-up.

Microalbuminuria, a phenotype of early DN, is one of the risk factors of macroalbuminuria (7,8). In addition, macroalbuminuria itself is known to be a risk factor resulting in renal function decline. In fact, a subset of microalbuminuric patients showed a rapid deterioration of renal function, which was evaluated with cystatin C–based eGFR (10). Another report (21) showed that normoalbuminuric type 2 diabetic patients had a decline in GFR similar to that in normal control subjects, while microalbuminuric patients showed more GFR loss for a 10-year follow-up. However, these reports (10,21) showed little information regarding DR. Microalbuminuria was indicated as a risk factor of DR in type 1 diabetic patients but not in type 2 diabetic patients (1). Thus, whether microalbuminuria itself or DR itself results in GFR decline must be examined to elucidate the exact and detailed clinical course of DN including both UAE and GFR changes (1).

Recently, DR has become known as a risk factor for all-cause mortality (22), cardiovascular event, and subclinical atherosclerosis (23) or cardiovascular disease (24). However, it is still obscure whether DR had some effects on UAE increase or GFR decline, especially in normoalbuminuric and low microalbuminuric diabetic patients. Thirty-eight Caucasian type 2 diabetic patients with macroalbuminuria showed higher rates of GFR decline during 6 years of observation when the patients had DR compared with the patients without DR (25). On the other hand, 25 Danish type 1 diabetic patients without macroalbuminuria revealed higher transition rates to macroalbuminuria when the patients had proliferative DR (13). In the current study, microalbuminuric patients with DR obviously revealed GFR decline, while normoalbuminuric patients with DR had a trend toward increase of UAE. In addition, hazard ratio was increased according to DR severity grade, especially in microalbuminuric patients. Therefore, we need to perform ophthalmological examination to detect DR carefully, especially in the patients with normo- or microalbuminuria, to identify persons at higher risk of developing macroalbuminuria. It has not been shown that DR itself is related to renal function decline, although some reports have shown that urinary abnormalities, microalbuminuria, or macroalbuminuria predicts DR (26), and microalbuminuria has been indicated to have a greater impact on predicting DR than GFR decline in type 2 diabetic patients (27).

There are few reports that both microalbuminuria and DR predict renal function loss. In Chinese populations, the reduction of eGFR of >50% or progression to eGFR <15 mL/min/1.73 m^2 or end-stage renal disease was predicted in the type 2 diabetic patients with microalbuminuria or DR compared with the patients with no complications (28). The risk of the renal outcome was obviously increased when both DR and microalbuminuria or macroalbuminuria were present (28). However, the report (28) did not show that the slope of GFR decline was related to the presence of microalbuminuria and DR. Therefore, the current study demonstrates for the first time that the rate of GFR decline was faster in patients with microalbuminuria and DR at the early stage of DN.

One of the reasons why UAE trended to be increased in normoalbuminuric patients with DR or GFR decreased in microalbuminuric patients with DR in the current study might be related to the severity of the renal histological changes including glomerular basement membrane (GBM) thickening and mesangial expansion. In fact, in normoalbuminuric type 1 diabetic patients, abnormal values of GBM thickness and mesangial expansion were more frequently seen in the patients with DR, and these histological changes aggravated according to DR grade (3). Another report (29) revealed that type 2 diabetic patients with macroalbuminuria showed more frequent Kimmelstiel-Wilson nodular lesions when the patients had proliferative DR.

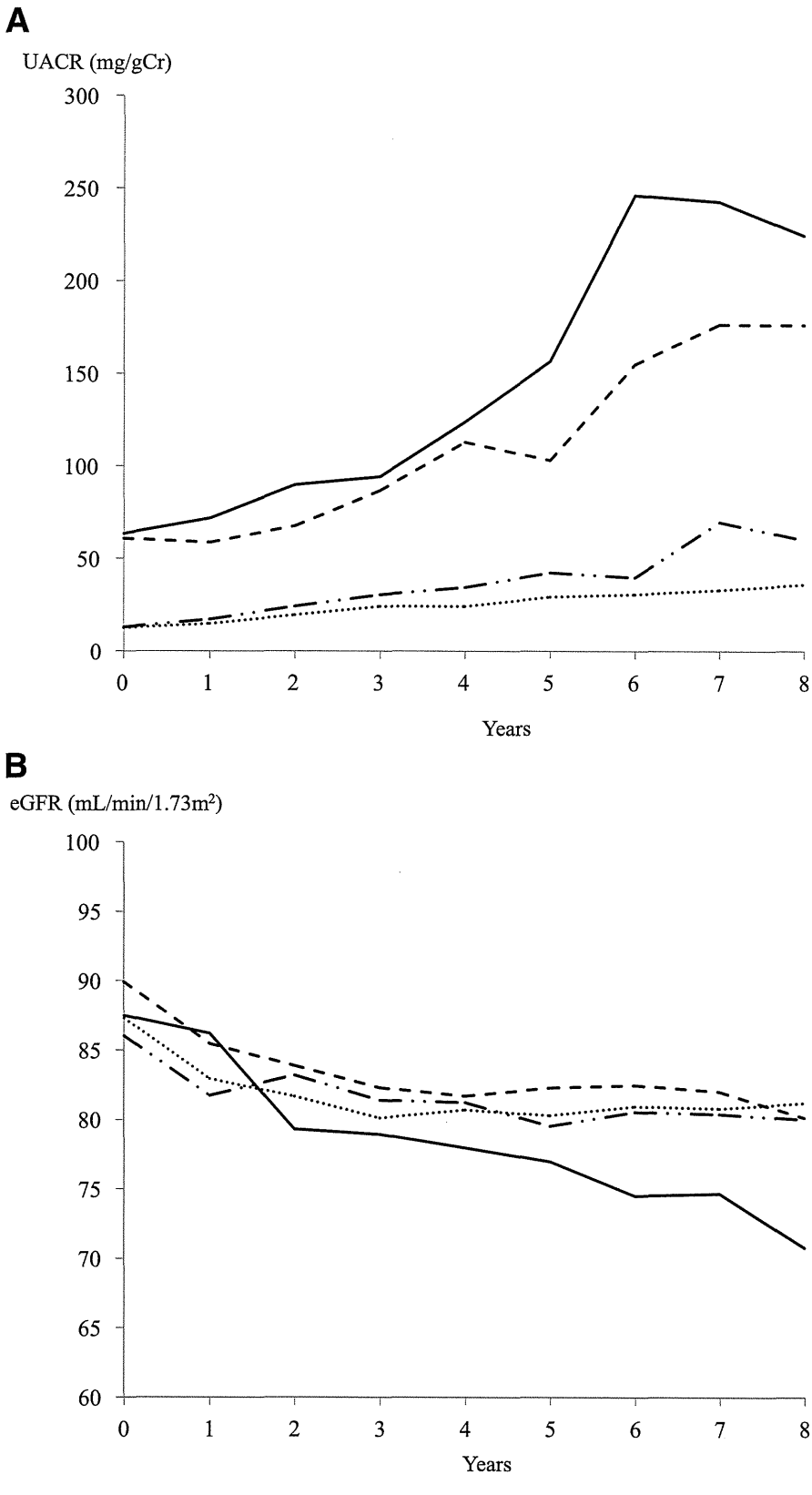

Figure 1—*The annual increase rate of UACR and decline rate of eGFR in each group. Dotted line, both normal; dash-dot line, retinopathy only; dashed line, albuminuria only; solid line, both abnormal. A: Two microalbuminuric groups showed a striking increase in UACR during the 8-year observation, although UACR in the two normoalbuminuric groups gradually increased more or less. B: The eGFR decline rate in the MA(DR+) group was significantly faster than that in the other three groups.*

The patients with nodular glomerulosclerosis frequently had an increase of serum creatinine within 5 years of follow-up (30). In addition, it was shown that renal histological changes were heterogeneous in microalbuminuric type 2 diabetic patients, and three histological categories of renal injury patterns were previously indicated (31). In the report (31), DR was present in all the patients with typical diabetic glomerular sclerosis. No proliferative DR was seen in the patients with a normal/near-normal pattern or atypical renal histological injury, while background DR was observed in 50 and 57% of patients, respectively. More recently, a link between quantitative assessment of the retinal vessel caliber size and change in glomerulopathy index including mesangial expansion and GBM thickening during 5 years follow-up was reported in normotensive normoalbuminuric Caucasian type 1 diabetic patients (32). Change in the retinal vessel caliber size has been speculated to be reflecting inflammation, endothelial dysfunction, and prevalence and incidence of DR (33). Therefore, DR might reflect renal histological severity as diabetic glomerulosclerosis regardless of albuminuria. In microalbuminuric Caucasian type 1 diabetic patients, the rate of annual GFR decline was related to renal histological change (34). In addition, in normo- and microalbuminuric Japanese type 2 diabetic patients, it was shown that UAE increased 5.6 years after the renal biopsy when renal histological changes, including mesangial expansion, were more severe (35). Thus, the patients with DR have more severe diabetic glomerular changes, which are followed by UAE increase or GFR decline compared with the patients without DR. Further examinations will be warranted to confirm the difference of histological changes among the four groups shown in the current study.

In the JDCS cohort, both blood pressure and glycemic control were risk factors of the occurrence of DR and the transition from normo- and low microalbuminuria to macroalbuminuria, whereas the duration of diabetes was a predictor for DR and smoking was a predictor for DN (9,17). In the previous study (9), progression to macroalbuminuria was independently associated with higher baseline HbA_{1c} and SBP levels in addition to an elevated baseline UACR; and smoking was a significant predictor of macroalbuminuria as well. These factors were also significant predictors of

Table 3—*Course of UAE according to baseline diabetic retinopathy*

	Final ACR (mg/gCr)							
	<30		30–150		150–300		≥300	
	n	%	*n*	%	*n*	%	*n*	%
No retinopathy								
Basal ACR <30 mg/gCr (*n* = 773)	593	76.7	158	20.4	13	1.7	9	1.2
Basal ACR 30–150 mg/gCr (*n* = 277)	89	32.1	124	44.8	30	10.8	34	12.3
Retinopathy								
Basal ACR <30 mg/gCr (*n* = 279)	188	67.4	69	24.7	14	5.0	8	2.9
Basal ACR 30–150 mg/gCr (*n* = 146)	37	25.3	64	43.8	23	15.8	22	15.1

ACR, albumin-to-creatinine ratio.

macroalbuminuria in the current study. Therefore, achievement of good glycemic and blood pressure control and smoking cessation education would be valuable to avoid GFR decline in type 2 diabetic patients, which will be examined in larger populations.

Our study has certain limitations. The first is that death before the onset of macroalbuminuria is a competing risk that potentially influences the association between macroalbuminuria and its risk factors. We handled such patients as censored because the mortality in this study was low (only 58 deaths [3.9%]) and seemed not to have much effect on the results. The second is that the prognosis of DR has not been examined yet. It is very important to clarify whether the presence of baseline microalbuminuria affects the progression of DR. Therefore, further study is warranted to analyze the prognosis of DR using the same cohort in the future. The final one is that the current study was established when angiotensin II receptor blockers (ARBs) were not widely used in our country, unfortunately. Since ARBs became available in 1998 in Japan, the number of renin-angiotensin system (RAS) inhibitor usage was small—12.3% at baseline—and was increased gradually to 28.4% at 8 years' follow-up based on each physician's decision—not on the protocol (9). It is well-known that RAS inhibitors including ACE inhibitors and ARBs remit microalbuminuria (36) or retard the onset of microalbuminuria (37). It is important to examine the detailed course of albuminuria or GFR prospectively, focusing on the effects of RAS inhibitors in a Japanese cohort in the future.

In conclusion, the presence of microalbuminuria and/or DR profoundly affects renal function in type 2 diabetic patients. Therefore, diabetologists and ophthalmologists should share their acquired information regarding DN and DR, even if it is at milder stages.

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T.M. researched data, contributed to the discussion, and wrote the manuscript. S.T. analyzed data. R.K. contributed to the discussion and reviewed and edited the manuscript. Y.O. analyzed data. Y.A. and N.Y. contributed to discussion. H.S. contributed to discussion and reviewed and edited the manuscript. H.Y. contributed to discussion. S.K. contributed to the discussion and reviewed and edited the manuscript. H.S. is the guarantor of this work and, as such, had full access to all 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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Risk of Cardiovascular Diseases Is Increased Even with Mild Diabetic Retinopathy

The Japan Diabetes Complications Study

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Objective: Diabetic retinopathy (DR) is linked to cardiovascular risk in diabetic patients. This study examined whether mild-stage DR is associated with risk of coronary heart disease (CHD) and stroke in type 2 diabetic patients of the Japan Diabetes Complications Study (JDCS).

Design: Prospective cohort study.

Participants: In the JDCS, there were 2033 Japanese persons with type 2 diabetes free of cardiovascular diseases at baseline.

Methods: Diabetic retinopathy was ascertained from clinical and photographic grading (70%) following the international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Incident CHD and stroke were followed up prospectively annually up to 8 years.

Main Outcome Measures: Eight-year incidence of CHD and stroke compared between persons with or without DR.

Results: After adjusting for traditional cardiovascular risk factors, persons with mild to moderate nonproliferative DR had a higher risk of CHD (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.17–2.97) and stroke (HR, 2.69; 95% CI, 1.03–4.86). Presence of retinal hemorrhages or microaneurysms was associated with risk of CHD (HR, 1.63; 95% CI, 1.04–2.56) but was not associated with stroke (P = 0.06). Presence of cotton-wool spots was associated with risk of incident stroke (HR, 2.39; 95% CI, 1.35–4.24) but was not associated with CHD (P = 0.66). When information about DR was added in the prediction models for CHD and stroke based on traditional cardiovascular risk factors, the area under the receiver operating curve improved from 0.682 to 0.692 and 0.640 to 0.677, and 9% and 13% of persons were reclassified correctly for CHD and stroke, respectively.

Conclusions: Type 2 diabetic patients with even a mild stage of DR, such as dot hemorrhages, are already at higher risk of CHD and stroke independent of traditional risk factors.

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Diabetic retinopathy (DR) is estimated to affect approximately 100 million people worldwide when extrapolated to the world diabetes population in 2010.[1] Increasing DR severity is associated with an increased risk of vision loss and risk of vision-threatening proliferative disease over time.[2,3] Presence of DR is not only one of the most common microvascular complications of diabetes, it also is an established predictor of cardiovascular diseases (CVDs). Diabetic patients with DR have been reported to be at higher risk of incident stroke[4–7] and coronary heart disease (CHD).[4,5,8] Kramer et al[9] reported that persons with any degree of DR are at 61% higher risk of CVD events and all-cause mortality independent of traditional risk factors based on the meta-analysis data of 20 epidemiologic studies.

However, there is limited knowledge regarding whether this association is observed consistently in Asian populations.[10,11] Sasaki et al[10] reported an association between the presence of any stage of DR and all-cause mortality in a Japanese type 2 diabetic cohort; detailed association between DR severity and specific CVD outcomes of stroke and CHD is unclear. Considering that duration of diabetes and glucose control or other risk factors are associated with severity of DR,[1] it is reasonable to speculate that people with a severe stage of microvascular complications such as advanced DR have macrovascular complications of CVD. What remains less understood is whether milder stage DR is associated with increased risk of CHD and stroke. There have been limited data reporting associations of early stage of DR and CVD and, if such as association exists, whether there is a continuous association between severity of DR and risk of CVD.[7,12]

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