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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

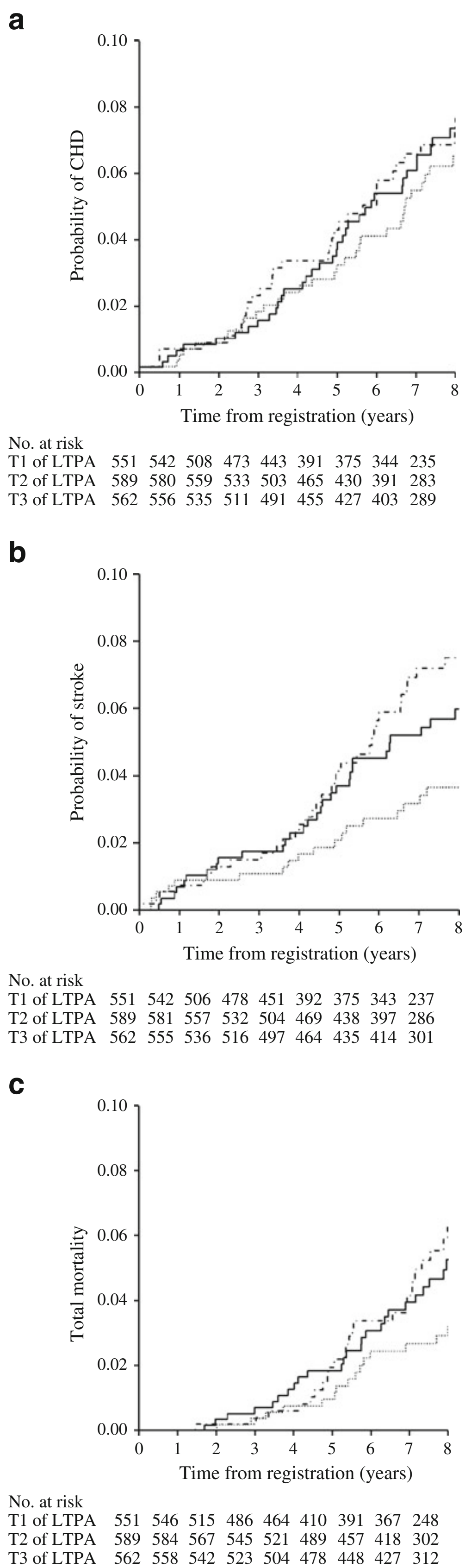
[b] Model 2, model 1 plus lifestyle factors (smoking, energy/ethanol intake, dietary fibre, saturated fatty acid and type of occupation)

[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



◀**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)

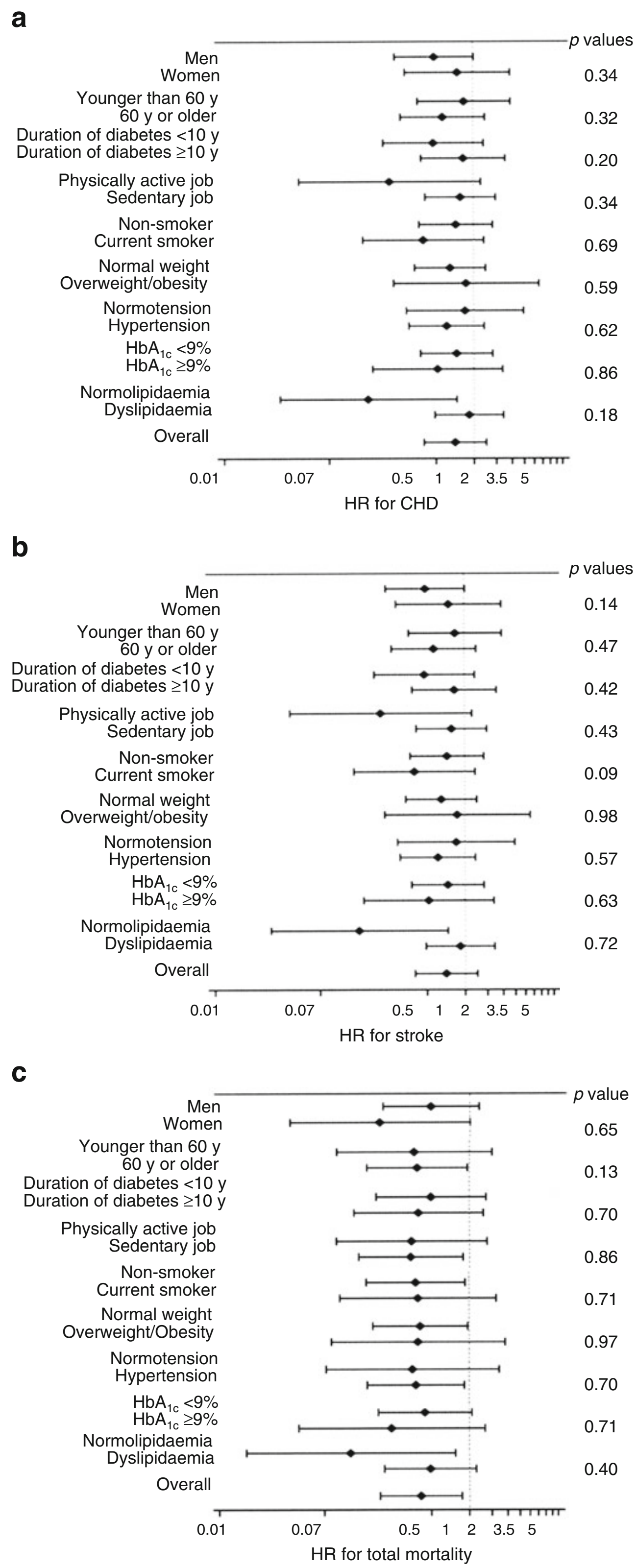
evaluated and scored was significantly associated only with cerebrovascular events and not with cardiac events [4].

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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