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ARTICLE

Leisure-time physical activity and development and progression of diabetic nephropathy in type 1 diabetes: the FinnDiane Study

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Abstract
Aims/hypothesis The aim of this study was to assess how physical activity predicts the development and progression of diabetic nephropathy in patients with type 1 diabetes.
Methods This prospective study (follow-up time 6.4±3.1 years) included 1,390 patients (48.5% men, mean age 37.0±12.4 years, duration of diabetes 20.4±12.3 years) participating in the nationwide multicentre Finnish Diabetic Nephropathy (FinnDiane) Study. Leisure-time physical activity (LTPA) was assessed using a validated self-report questionnaire. Renal status was defined according to standard clinical cut-off values for urinary AER.
Results The total amount of LTPA was not associated with progression in renal status. For the intensity of LTPA, however, the 10 year cumulative progression rate was 24.0% (95% CI 18.8, 28.8), 13.5% (95% CI 10.3, 16.6) or 13.1% (95% CI 10.3%, 16.6%; p=0.01) of the patients with low, moderate or high intensity LTPA. This pattern was similar to that for the development of de novo microalbuminuria. Corresponding progression rates for LTPA frequency of <1, 1–2 or >2 sessions/week was 24.7% (95% CI 18.3, 30.7), 14.7% (95% CI 10.2, 19.0) or 12.6% (95% CI 9.4, 15.7), respectively (p=0.003).
Conclusions/interpretation This study demonstrates for the first time in a prospective setting the relationship between physical activity and the risk of diabetic nephropathy in patients with type 1 diabetes. The data suggest that physical activity, and in particular its intensity, may have an impact

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on the initiation and progression of diabetic nephropathy in type 1 diabetes.

Keywords Exercise · Nephropathy · Physical activity · Type 1 diabetes

Abbreviations

CVD	Cardiovascular disease
ESRD	End-stage renal disease
FinnDiane Study	The Finnish Diabetic Nephropathy Study
LTPA	Leisure-time physical activity
MET	Metabolic equivalent
UAER	Urinary AER

Introduction

Type 1 diabetes is associated with an increased risk of premature death due to late diabetic complications, most importantly diabetic nephropathy. However, we recently showed that patients with type 1 diabetes without signs of renal involvement have a mortality rate no different from that of a non-diabetic, age- and sex-matched population [1], thus highlighting the importance of preserving normoalbuminuria in type 1 diabetes. To decrease the risk of renal disease, a multi-intervention approach is usually needed to optimise glycaemic control and the control of BP and lipids. Pharmacological means are often required, but lifestyle factors are also likely to be important.

Physical activity may improve the risk factor profile of patients with type 1 diabetes [2]. We previously showed that sedentary women with type 1 diabetes have worse glycaemic control than those who achieve the general recommendations for regular physical activity [3]. However, no prospective epidemiological studies have assessed the level of physical activity and the development of diabetic microvascular complications in patients with type 1 diabetes. The available cross-sectional data show, unsurprisingly, that a higher degree of diabetic late complications is associated with lower physical activity [4, 5]. However, the causal relationship is unclear and, in the case of overt diabetic nephropathy, probably due to disease-related exercise intolerance. Nevertheless, we previously showed that patients with microalbuminuria report undertaking physical activity of lower intensity compared with normoalbuminuric patients with type 1 diabetes [4]. Although cross-sectional, this observation suggested that there might be a causal relationship.

The prospective, nationwide, multicentre Finnish Diabetic Nephropathy (FinnDiane) Study investigates clinical, genetic, biochemical and lifestyle risk factors for diabetic nephropathy in patients with type 1 diabetes. Information on leisure-time physical activity (LTPA) has been collected from a large number of patients. In the present study, we report the relationship of baseline LTPA with the development of de novo microalbuminuria and the progression of renal disease in 1,424 patients with type 1 diabetes followed for a mean of 6.4±3.1 years.

Methods

This study forms part of the ongoing FinnDiane Study, which was previously described in detail [6]. In brief, the FinnDiane Study is searching for clinical, genetic, environmental and metabolic risk factors for diabetic complications, with a special emphasis on diabetic nephropathy, in patients with type 1 diabetes. At baseline and follow-up, data on diabetic complications and clinical and laboratory measurements were collected during regular visits to the attending physician using standardised questionnaires and by clinical investigation. All patients gave written informed consent to participate. The local ethical committees of the participating centres approved the study protocol and the study was performed in accordance with the Declaration of Helsinki.

Anthropometric data (weight, height, and waist and hip circumferences) were collected by a trained nurse. Blood pressure was measured twice with 2 min intervals in the sitting position after a 10 min rest. Alcohol consumption (one dose of alcohol equals 12 g) and smoking were assessed using questionnaires. Fasting blood samples were collected and analysed for HbA_{1c} and serum lipids.

LTPA was assessed using a previously validated self-report questionnaire [7, 8]. The amount of LTPA is given in units of metabolic equivalent (MET) ×h/week. The patients were classified as sedentary (<10 MET ×h/week), moderately active (10–40 MET ×h/week) and active (>40 MET ×h/week). The intensity of LTPA was defined as follows: low intensity, no self-reported subjective shortness of breath and no sweating; moderate intensity, a moderate degree of self-reported subjective shortness of breath and sweating; and high intensity, a high degree of subjective shortness of breath and sweating.

Renal status was defined according to the urinary AER (UAER) for at least two out of three consecutive 24 h or timed overnight urine collections: normoalbuminuria, UAER <20 μg/min or <30 mg/24 h; microalbuminuria, ≥20 and <200 μg/min or ≥30 and <300 mg/24 h; and macroalbuminuria, ≥200 μg/min or ≥300 mg/24 h. Diabetic nephropathy was defined as macroalbuminuria or end-stage renal disease (ESRD). Progression in renal status during follow-up was defined as any shift to a higher albuminuria class or development of ESRD, defined as requiring dialysis or a kidney transplant. Diabetic retinopathy was defined based on fundus photography and by a history of retinal laser treatment. Cardiovascular disease (CVD) was defined as a clinically verified myocardial infarction, coronary

revascularisation procedure, stroke, ischaemic limb amputation or a peripheral artery revascularisation procedure.

The LTPA questionnaire was introduced at the beginning of the year 2000. Up to 2011, a total of 62% of the patients with type 1 diabetes had answered the questionnaire. The clinical characteristics of patients that answered the LTPA questionnaire were comparable with those that did not. For this study, we identified all patients in the FinnDiane database with baseline LTPA data and data on renal status at both baseline and follow-up (N=1,782). Patients with baseline ESRD (n=79), unknown renal status (n=109) or unknown renal progression status (n=170) were excluded. Type 1 diabetes was restricted to a diagnosis of diabetes before the age of 35 years and permanent insulin treatment initiated within 1 year of diagnosis. Finally, the study population comprised 1,424 patients. None of the patients had comprehensive data available for all components of LTPA, but we aimed to use the maximum amount of available data. Therefore, the total number of patients differed somewhat in the analyses of total amount, intensity, frequency and duration of LTPA. A total of 1,390 patients were included in our main analyses of intensity of LTPA and progression in renal status.

Statistical analyses were performed using SPSS Statistics version 21 (IBM, Armonk, NY, USA) and SAS version 9.3 (SAS Institute, Cary, NC), and figures were drawn using GraphPad Prism version 5 (GraphPad, La Jolla, CA, USA). Continuous variables are given as means±SD if normally distributed, otherwise as median with interquartile range. Categorical variables are given as percentages. Between-group differences were analysed using ANOVA for normally distributed variables and with the Kruskal–Wallis test for non-normally distributed variables. Categorical variables were analysed using the χ^2 test. Trend-test p values were used when appropriate. The cumulative progression rate was estimated using the Kaplan–Meier method, and the logrank test was used to test for between-group differences. For multivariate analyses, Cox proportional hazard survival regression was used. A p value of <0.05 was considered statistically significant.

Results

Of the 1,424 patients included, 48.5% were men and at baseline the mean age was 37.0±12.4 years, the duration of diabetes was 20.4±12.3 years, the BMI was 25.0±3.4 kg/m^2, systolic BP was 132±16 mmHg and HbA_{1c} was 8.3±1.4% (67±15 mmol/mol). Of the total patient cohort, 42.6% were ever-smokers (current or previous) and 5.0% had CVD. Regarding renal status, 1,073 patients had normal UAER, 185 had microalbuminuria and 166 had macroalbuminuria.

At baseline, the median LTPA of the entire population was 17.9 (8.4–34.2) MET ×h/week. Table 1 shows the baseline

Table 1 Relationship between clinical characteristics and total LTPA

Characteristic	Sedentary	Moderately active	Active	p value
n	414	704	264	–
Male (%)	50.5	46.6	48.1	0.453
Age (y)	37.8±12.8	36.7±12.0	36.0±12.3	0.181
Duration of diabetes (y)	20.4±12.6	20.1±12.0	20.2±12.5	0.905
BMI (kg/m^2)	25.3±3.6	24.9±3.4	24.7±3.0	0.101
WHR, men	0.92±0.07	0.90±0.07	0.89±0.06	<0.001
WHR, women	0.83±0.07	0.82±0.06	0.81±0.07	0.189
SBP (mmHg)	133±16	131±16	132±17	0.476
DBP (mmHg)	79±10	78±9	79±9	0.889
HbA_{1c} (%)	8.5±1.4	8.2±1.4	8.3±1.5	0.002
HbA_{1c} (mmol/mol)	70±15	66±15	67±16	
Total cholesterol (mmol/l)	4.8±0.8	4.8±0.8	4.8±0.9	0.865
HDL-cholesterol (mmol/l)	1.37±0.36	1.42±0.37	1.41±0.40	0.069
LDL-cholesterol (mmol/l)	2.89±0.76	2.91±0.78	2.89±0.81	0.871
Triacylglycerol (mmol/l)	1.05 (0.78–1.38)	0.94 (0.73–1.29)	0.94 (0.72–1.29)	0.011
AHT (%)	36.5	27.9	29.3	0.010
β-blocker (%)	10.9	8.0	3.8	0.001
CVD (%)	5.6	4.3	4.6	0.609
Retinopathy (%)	50.6	45.8	44.0	0.079
Diabetic nephropathy (%)	14.0	10.4	9.8	0.067
Ever-smokers (%)	51.4	39.8	38.7	<0.001
Alcohol consumption (doses/week)	3.0 (0.0–7.0)	2.0 (0.0–6.4)	1.5 (0.0–4.8)	0.001

Data are means±SD, medians (interquartile range) or percentages

AHT, antihypertensive medication; DBP, diastolic BP; SBP, systolic BP; y, years

clinical characteristics regarding LTPA. A low level of LTPA was associated with abdominal obesity, worse glycaemic control, smoking, a greater use of alcohol, higher level of triacylglycerol and a more frequent use of antihypertensive drugs. There was no association between LTPA and sex, age or duration of diabetes. Table 2 and electronic supplementary material (ESM) Tables 1 and 2 show the relationships between clinical characteristics and the different components of LTPA.

The mean follow-up time was 6.4±3.1 years, during which 149 patients showed progression in their renal status: 72 normoalbuminuric patients developed microalbuminuria, 35 microalbuminuric patients developed macroalbuminuria and 42 macroalbuminuric patients developed ESRD. Table 3 shows that at baseline such progressors were older, more often men, more obese and had higher BP, worse glycaemic control and lipid profile, and more often had a history of smoking and consumed more alcohol.

Progressors and non-progressors of renal status had similar total LTPA of 17.6 (6.2–31.9) and 17.9 (8.4–34.6) MET ×h/week, respectively (p=0.544). Likewise, patients with a sedentary, moderately active and active level of LTPA had similar 10 year cumulative progression rates of 15.7% (95% CI 11.2, 20.0), 16.2% (95% CI 12.6, 19.6) and 12.0% (95% CI 6.7, 17.0) (p=0.67), respectively. However, the intensity of LTPA was associated with progression in renal status: in patients with a low intensity of LTPA, the 10 year cumulative progression rate was 24.0% (95% CI 18.8, 28.8); in those with a moderate intensity of LTPA, it was 13.5% (95% CI 10.3, 16.6); and in those with a high intensity of LTPA, it was 13.1% (95% CI 10.3, 16.6) (p=0.01). Similarly, patients with an LTPA frequency of <1, 1–2 or >2 times per week had a 10 year cumulative risk of progression in renal status of 24.7% (95% CI 18.3, 30.7), 14.7% (95% CI 10.2, 19.0) or 12.6% (95% CI 9.4, 15.7), respectively (p=0.003). The duration of LTPA was not associated with progression in renal status. Figure 1 shows Kaplan–Meier curves showing the relationship between different components of LTPA and the progression in renal status.

To explore the possibility of physical inactivity bias concerning pre-existing baseline renal disease, we separately analysed progression from normo- to microalbuminuria, that is, the development of de novo microalbuminuria. The total amount of LTPA was not associated with progression to microalbuminuria. Interestingly, LTPA intensity seemed to be associated with progression to microalbuminuria because the Kaplan–Meier analysis showed that the initial progression rate was more rapid, although it was attenuated towards the end of the follow-up in the low intensity group compared with the medium and high intensity groups. During 8 years of follow-up, the cumulative progression rate from normo- to

Table 2 Relationship between clinical characteristics and intensity of LTPA

Characteristic	Low intensity	Moderate intensity	High intensity	p value
n	339	746	310	–
Male (%)	48.4	39.5	70.0	<0.001
Age (y)	41.1±12.7	37.6±12.0	30.6±10.3	<0.001
Duration of diabetes (y)	24.1±12.7	20.7±12.1	15.0±10.6	<0.001
BMI (kg/m^2)	25.7±3.9	24.9±3.4	24.6±2.9	<0.001
WHR, men	0.93±0.08	0.91±0.07	0.89±0.06	<0.001
WHR, women	0.84±0.07	0.81±0.06	0.81±0.07	<0.001
SBP (mmHg)	135±17	132±17	130±15	0.001
DBP (mmHg)	79±10	79±9	78±9	0.336
HbA_{1c} (%)	8.6±1.4	8.3±1.3	8.2±1.5	<0.001
HbA_{1c} (mmol/mol)	70±15	67±15	65±16	
Total cholesterol (mmol/l)	4.9±0.9	4.9±0.8	4.6±0.9	<0.001
HDL-cholesterol (mmol/l)	1.41±0.40	1.42±0.38	1.37±0.35	0.141
LDL-cholesterol (mmol/l)	2.94±0.80	2.97±0.75	2.71±0.78	<0.001
Triacylglycerol (mmol/l)	1.06 (0.79–1.45)	0.96 (0.73–1.29)	0.90 (0.74–1.27)	0.003
AHT medication (%)	44.6	30.4	17.5	<0.001
β-blocker (%)	16.1	7.4	1.6	<0.001
Retinopathy (%)	61.5	48.2	28.5	<0.001
CVD (%)	10.7	4.1	0.7	<0.001
Diabetic nephropathy (%)	22.4	9.7	3.9	<0.001
LTPA (MET ×h/week)	9.6 (3.1–18.6)	18.7 (9.4–34.6)	28.9 (16.1–47.3)	<0.001
Ever-smokers (%)	57.4	41.6	34.1	<0.001
Alcohol consumption (doses/week)	2.5 (0.0–8.0)	2.0 (0.0–5.0)	3.0 (0.0–7.0)	0.016

Data are means±SD, medians (interquartile range) or percentages

AHT, antihypertensive; DBP, diastolic BP; SBP, systolic BP; y, years

Table 3 Clinical characteristics for any progression in renal status

Characteristic	Non-progressors	Progressors	*p* value[a]
n	1,275	149	–
Male (%)	47.1	61.1	0.001
Age (y)	36.7±12.4	39.9±11.6	0.003
Duration of diabetes (y)	19.9±12.3	24.2±11.9	<0.001
BMI (kg/m^2)	24.9±3.3	25.8±4.3	0.002
WHR, men	0.90±0.07	0.94±0.07	<0.001
WHR, women	0.82±0.06	0.84±0.08	0.018
SBP (mmHg)	132±16	137±19	<0.001
DBP (mmHg)	78±9	81±9	<0.001
HbA_{1c} (%)	8.3±1.4	9.0±1.5	<0.001
HbA_{1c} (mmol/mol)	67±15	75±17	
Total cholesterol (mmol/l)	4.8±0.9	5.0±0.9	0.019
HDL-cholesterol (mmol/l)	1.41±0.37	1.37±0.41	0.243
LDL-cholesterol (mmol/l)	2.89±0.77	2.98±0.86	0.184
Triacylglycerol (mmol/l)	0.95 (0.73–1.29)	1.21 (0.85–1.80)	<0.001
AHT medication (%)	28.3	55.4	<0.001
β-blocker (%)	7.0	19.6	<0.001
Retinopathy (%)	44.5	72.7	<0.001
CVD (%)	4.4	10.8	0.001
Diabetic nephropathy (%)	9.7	28.2	<0.001
LTPA (MET ×h/week)	17.9 (8.4–34.6)	17.6 (6.2–31.9)	0.544
Ever-smokers (%)	41.3	65.3	<0.001
Alcohol consumption (doses/week)	2.0 (0.0–6.0)	3.0 (0.05–8.5)	0.044

Data are means±SD, medians (interquartile range) or percentages

AHT, antihypertensive; DBP, diastolic BP; SBP, systolic BP; y, years

[a] *p* values were calculated for univariate Cox regression analyses with progression as the outcome

microalbuminuria was 15.4% (95% CI 9.4, 21.0), 6.9% (95% CI 4.5, 9.3) and 5.9% (95% CI 2.1, 9.6) in the low, moderate and high intensity groups, respectively (p=0.047, logrank test). However, the differences flattened out at the end of follow-up. Frequency or duration of LTPA was not associated with progression to microalbuminuria.

Table 4 shows a Cox regression model for progression in renal status, showing the HRs for low vs moderate and high intensity of LTPA. For progression to micro- or macroalbuminuria, low intensity LTPA was associated with a higher rate of progression. This finding was unaffected by static confounders such as duration of diabetes, sex and smoking. In contrast, confounding factors (HbA_{1c}, BP, triacylglycerol and BMI) that could potentially be influenced by LTPA, incrementally decreased this association to a non-significant level. For the development of de novo microalbuminuria, a similar finding was observed, with comparable HRs but non-significant p values. ESM Tables 3–5 show corresponding Cox regression models for the frequency, duration and total amount of LTPA. For total LTPA, after correction for both static and dynamic confounders, the development of de novo microalbuminuria was significantly higher in sedentary patients compared with patients with moderately active or active levels of LTPA, at 1.90 (95% CI 1.04, 3.49) (ESM Table 5).

Discussion

We show that the intensity of LTPA may play a role in the initiation and progression of diabetic kidney disease. Of the other components of LTPA, the frequency was also associated with progression. The total amount or duration of LTPA did not affect the development or progression of diabetic kidney disease.

The beneficial effects of physical activity in the general population, as well as in patients with type 2 diabetes, are well known. For type 1 diabetic patients, it was previously shown that the total amount of LTPA is inversely related to mortality [9]. Mortality in patients with diabetes is usually due to diabetic late complications. Diabetic nephropathy has been shown to explain practically all of the excess mortality in type 1 diabetic patients [1, 10]. Therefore, it would be expected that a beneficial effect of LTPA on mortality would involve a reduced risk of diabetic complications, especially nephropathy. So far, only cross-sectional studies into LTPA and diabetic complications in type 1 diabetes are available [4, 5], but the causal relationships are unclear. However, our previous finding of a reduced intensity of LTPA in patients with micro- compared with normoalbuminuria suggested that low LTPA intensity might precede microalbuminuria [4]. In the present study, we were able to show this finding in a longitudinal setting.

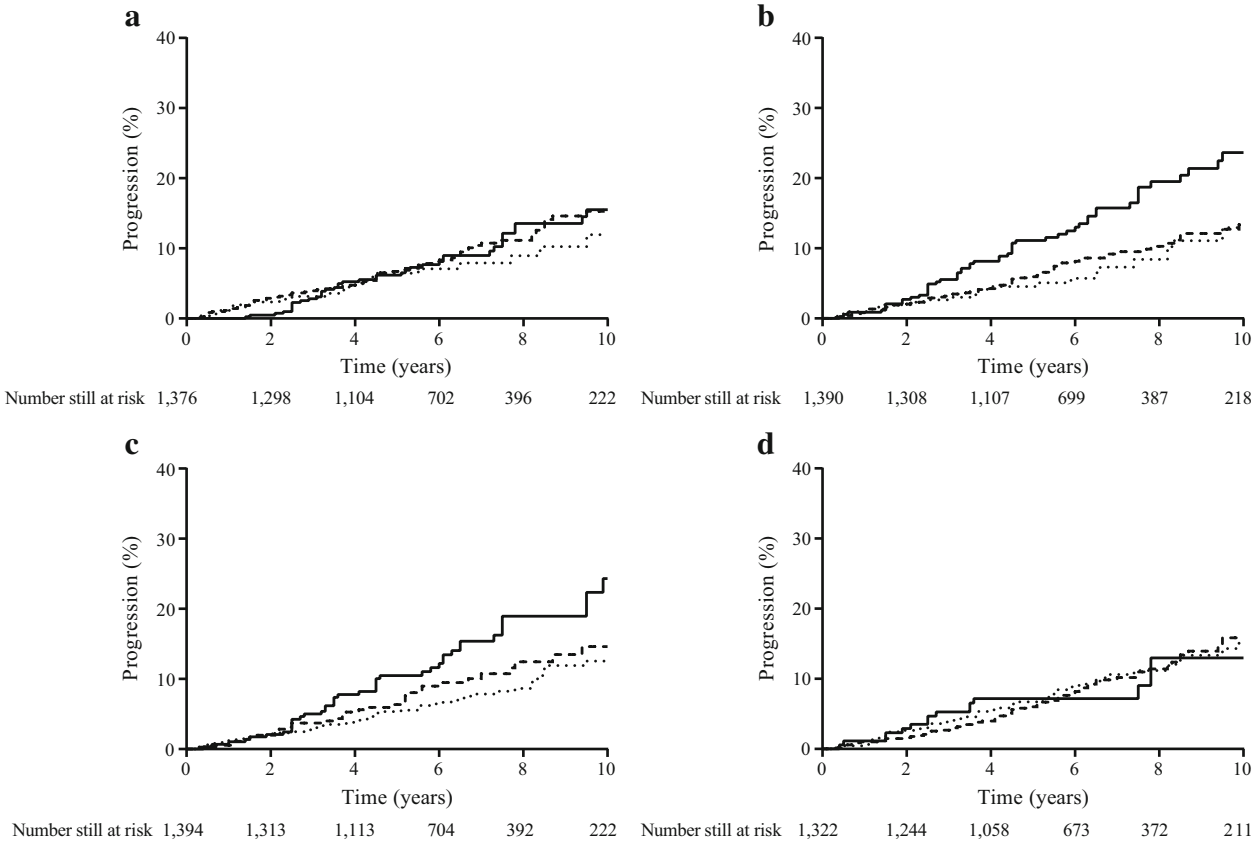

Fig. 1 Kaplan–Meier curves for total LTPA and components of LTPA regarding progression in renal status. Progression in renal status was defined as any shift to a higher albuminuria class or to ESRD. Sedentary, LTPA <10 MET ×h/week; moderately active, LTPA 10–40 MET ×h/week; active, LTPA >40 MET ×h/week. (**a**) Total LTPA. Continuous line, sedentary; dashed line, moderately active; dotted line, active (overall p=0.67). (**b**) Intensity of LTPA. Continuous line, low intensity; dashed line, moderately intensity; dotted line, high intensity (overall p=0.01). (**c**) Frequency of LTPA. Continuous line, <1 time/week; dashed line, 1–2 times/week; dotted line, >2 times/week (overall p=0.003). (**d**) Duration of LTPA. Continuous line, 0–30 min/time; dashed line, 30.1–60 min/time; dotted line, >60 min/time (overall p=0.86)

Table 4 Cox regression models showing the HR for low vs moderate and high intensity LTPA for progression in renal status

Model	Progression to micro- or macroalbuminuria		Progression to microalbuminuria		Progression to ESRD	
	HR[a] (95% CI)	*n*	HR[a] (95% CI)	*n*	HR[a] (95% CI)	*n*
1	1.79 (1.19, 2.69)	1,230	1.54 (0.92, 2.59)	1,049	1.17 (0.63, 2.17)	160
2	1.58 (1.04, 2.41)	1,211	1.41 (0.83, 2.41)	1,035	1.20 (0.64, 2.27)	159
3	1.53 (1.00, 2.32)	1,198	1.31 (0.77, 2.23)	1,024	1.23 (0.62, 2.46)	154
4	1.46 (0.96, 2.24)	1,190	1.26 (0.73, 2.17)	1,016	1.28 (0.64, 2.56)	153
5	1.43 (0.93, 2.22)	1,160	1.31 (0.76, 2.27)	989	1.36 (0.67, 2.79)	147
6	1.48 (0.96, 2.29)	1,156	1.22 (0.70, 2.14)	986	1.40 (0.67, 2.94)	147

Model 1: low intensity LTPA

Model 2: Model 1 + sex, duration of diabetes and current smoking

Model 3: Model 2 + HbA_{1c}

Model 4: Model 2 + mean arterial pressure

Model 5: Model 2 + triacylglycerol

Model 6: Model 2 + BMI

LTPA, leisure-time physical activity

[a] For low intensity LTPA

Traditionally, endurance exercise has been regarded as the most beneficial for health. Recent studies, however, show that the intensity of LTPA also might be important. Astonishingly, as little as three minutes of intense exercise per week has been shown to improve insulin action [11] and intensive training of short duration improved short-term glycaemia in patients with type 2 diabetes [12]. Life expectancy was longer with vigorous than with non-vigorous exercise [13, 14]. The intensity of LTPA was more important than the total energy output in preventing hypertension and avoiding premature mortality [15]. LTPA intensity was also associated with a reduced risk of CHD [16], as well as reduced levels of subcutaneous fat and WHR [17], independently of the total energy expenditure of LTPA. These findings suggest that mechanisms other than merely higher energy consumption are involved. There are, however, also data on a similar risk reduction for the development of type 2 diabetes for both vigorous physical activity and walking, where the total energy expenditure is comparable [18].

Possible mechanisms by which physical activity may prevent the development of diabetic complications are lowering of BP and improvements to lipid profile, glycaemic control, insulin sensitivity and endothelial function. An effect mediated by changes in insulin sensitivity is especially appealing because insulin resistance is thought to play a major role in the development of diabetic complications, including microalbuminuria [19, 20]. Physical activity has been further shown to have anti-inflammatory effects, and chronic low-grade inflammation has been implicated in the pathogenesis of diabetic complications [21, 22]. Finally, increased UAER has been proposed as a marker of global vascular dysfunction in patients with type 1 diabetes, according to the Steno hypothesis [23], and exercise training interventions have been shown to improve endothelial function in patients with type 1 and type 2 diabetes [24, 25]. In line with this, our multivariate analyses show that HbA_{1c}, BP and BMI eliminated the association between LTPA and progression of renal disease, which may indicate that a possible protective role of LTPA is mediated by these dynamic confounders upon which LTPA itself may have a positive effect.

The strengths of this study are the prospective study design including a large number of patients and a previously validated LTPA questionnaire [7, 8]. A weakness is the possible reporting bias due to the assessment of LTPA by a self-report questionnaire. In contrast, objective measures of LTPA are not feasible with such a large number of patients and it should be taken into account that objective measures may also have intrinsic activity bias.

In conclusion, we examined for the first time the longitudinal relationship between physical activity and the development and progression of diabetic nephropathy in type 1 diabetes. Our results suggest that LTPA, especially of high intensity, may prevent development and progression of diabetic nephropathy in patients with type 1 diabetes.

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Contribution statement CF, JW, LMT, MR-B, MS, NT, DG, HOT and P-HG were involved in data collection; JW, HKT and VH analysed the data; and JW and HKT wrote the manuscript draft. All authors contributed to and approved of the final submitted version of the manuscript. JW takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

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