Physical Activity Reduces Risk of Premature Mortality in Patients With Type 1 Diabetes With and Without Kidney Disease

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OBJECTIVE

The aims of the study were to assess how baseline leisure-time physical activity (LTPA) and its exercise components intensity, duration, and frequency are associated with all-cause and cardiovascular mortality in patients with type 1 diabetes *1*) overall, *2*) stratified by presence or absence of chronic kidney disease (CKD), and *3*) stratified by sex.

RESEARCH DESIGN AND METHODS

The study design was prospective and observational and included 2,639 patients with type 1 diabetes from the ongoing nationwide multicenter Finnish Diabetic Nephropathy (FinnDiane) Study. Mean follow-up time was 11.4 ± 3.5 years. LTPA was assessed by using a validated self-report questionnaire. Three hundred ten patients (11.7%) had CKD defined as an estimated glomerular filtration rate of ≤60 mL/min/1.73 m^2.

RESULTS

During follow-up, 270 deaths occurred. LTPA and all its components were associated with all-cause mortality, even after adjustment for the potential confounders sex, diabetic nephropathy, duration of diabetes, age at onset of diabetes, systolic blood pressure, triglycerides, BMI, and HbA_{1c}. Only exercise intensity was associated with cardiovascular mortality after adjustment for the confounders. Of the patients with CKD, 127 died during follow-up. The total amount of LTPA and exercise frequency were independently associated with lower risk of all-cause mortality when adjusted for covariates.

CONCLUSIONS

Exercise is associated with a lower risk of premature all-cause and cardiovascular mortality in patients with type 1 diabetes. This study also demonstrates that physical activity is associated with a lower risk of mortality in patients with type 1 diabetes and CKD.

A high level of leisure-time physical activity (LTPA) or fitness is associated with a reduced risk of premature mortality in the general population and in individuals with type 2 diabetes (1,2), but whether this is true for patients with type 1 diabetes has not yet been determined because the available evidence is limited. Only a few prospective studies have explored the association of LTPA and mortality in type 1 diabetes, and none have been performed in patients with type 1 diabetes and chronic kidney disease (CKD).

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We have previously demonstrated that the intensity of LTPA is associated with the development and progression of diabetic nephropathy in patients with type 1 diabetes (3). Similarly, a higher amount of LTPA was associated with a lower risk of incident cardiovascular events (4). Because we have previously shown that diabetic nephropathy accounts for the increased mortality observed in type 1 diabetes (5), we hypothesized that exercise also reduces the risk of premature mortality in these patients.

Of the few previous studies that explored mortality and type 1 diabetes, the Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality Study demonstrated that sedentary men with type 1 diabetes have a higher mortality rate than active men. A similar pattern, although not statistically significant, was seen in women (6,7). Moreover, a report from the EURODIAB Prospective Complications Study demonstrated a borderline inverse association between physical activity and all-cause mortality in type 1 diabetes when both sexes were combined (8).

Exercise is already recommended for patients with CKD and those who undergo dialysis, although conclusive end point studies are scarce (9–12), and even more so for individuals with type 1 diabetes. Therefore, the aim of the current study was to fill in this gap and to assess how baseline LTPA and its various components are associated with all-cause and cardiovascular mortality in patients with type 1 diabetes with and without CKD as well as when stratified by sex.

RESEARCH DESIGN AND METHODS

This prospective and observational study comprised 2,369 patients participating in the nationwide Finnish Diabetic Nephropathy (FinnDiane) Study, which has been previously described in detail (13). The FinnDiane Study was initiated in 1997, and to date, >5,000 patients have participated. The LTPA questionnaire was introduced in the beginning of 2000, and in this substudy, we included all patients with available LTPA data. Type 1 diabetes was defined as a diagnosis of diabetes before the age of 40 years and permanent insulin treatment initiated within 1 year of diagnosis. Patients with not-yet-classifiable renal disease were excluded (n = 93). Before participation, all patients gave informed consent, and the study protocol was approved by the Ethics Committee of the Helsinki University Hospital and confirmed by the local ethics committees. The study was conducted according to the Declaration of Helsinki.

The primary end point of this study was death as a result of any cause through the end of 2014 and identified through a search of the Finnish National Death Registry and the local center databases. A major cardiovascular event was the cause of death in 28% of the patients. A cardiovascular event was defined as clinically verified myocardial infarction (ICD-8 and ICD-9 codes 410–412, ICD-10 codes I21–I23) or either an ischemic or a hemorrhagic stroke (ICD-8 and ICD-9 codes 430–434, ICD-10 codes I60–I64).

Renal function (estimated glomerular filtration rate [eGFR]) was estimated by using the Chronic Kidney Disease Epidemiology Collaboration equation (14). CKD was defined as an eGFR ≤60 mL/min/1.73 m^2 or end-stage renal disease (ESRD) (defined as undergoing dialysis or having received a kidney transplant). However, patients with a kidney transplant and eGFR >60 mL/min/1.73 m^2 (n = 53) were not defined as having CKD. Patients with CKD were grouped as having CKD without ESRD, undergoing dialysis, or having a kidney transplant. The baseline urinary albumin excretion rate (UAER) was defined as follows: normal UAER as <20 μg/min and <30 mg/24 h (n = 1,633), microalbuminuria as ≥20 and <200 μg/min or ≥30 mg/24 h and <300 mg/24 h (n = 312), and macroalbuminuria as UAER ≥200 μg/min or ≥300 mg/24 h (n = 271) in at least two of three consecutive 24-h or timed overnight urine collections.

Data on medication, cardiovascular status, and diabetic complications were registered by a standardized questionnaire and verified from the medical files by the patient's attending physician. Data on smoking status were collected by a self-administered questionnaire. Anthropometric data were collected by a trained

Table 1—Baseline characteristics according to vital status during follow-up and stratified by death as a result of any cause and cardiovascular death

		Death			
Characteristic	Alive	Any cause	P value	Cardiovascular	P value
Participants (n)	2,099	270		75	
Male sex (%)	47.0	60.7	<0.001	56.0	0.124
Age (years)	38.8 ± 12.2	50.1 ± 10.5	<0.001	48.5 ± 9.5	<0.001
Duration of diabetes (years)	21.9 ± 12.4	33.6 ± 10.8	<0.001	34.2 ± 9.1	<0.001
BMI (kg/m^2)	25.2 ± 3.6	25.5 ± 4.2	0.151	25.7 ± 4.1	0.22
WHR men	0.92 ± 0.07	0.95 ± 0.08	<0.001	0.96 ± 0.08	<0.001
WHR women	0.82 ± 0.06	0.86 ± 0.08	<0.001	0.86 ± 0.05	<0.001
SBP (mmHg)	134 ± 18	146 ± 23	<0.001	147 ± 22	<0.001
DBP (mmHg)	79 ± 10	78 ± 11	0.235	79 ± 12	0.747
HbA_{1c} (%)	8.3 ± 1.4	8.6 ± 1.4	<0.001	9.0 ± 1.4	<0.001
HbA_{1c} (mmol/mol)	67 ± 15	70 ± 15	<0.001	75 ± 15	<0.001
Total cholesterol (mmol/L)	4.79 ± 0.86	4.91 ± 0.99	0.027	4.83 ± 0.91	0.661
HDL cholesterol (mmol/L)	1.44 ± 0.40	1.38 ± 0.45	0.047	1.23 ± 0.43	<0.001
Triglycerides (mmol/L)	0.96 (0.74–1.33)	1.25 (0.92–1.69)	<0.001	1.42 (1.07–2.02)	<0.001
AHT (%)	34.3	78.7	<0.001	85.3	<0.001
β-Blockers (%)	10.0	45.6	<0.001	54.7	<0.001
Ever smokers (%)	44.2	59.0	<0.001	52.1	0.185
LTPA (MET-h/week)	17.2 (6.7–33.8)	8.6 (0–26.7)	<0.001	8.0 (0–25.9)	<0.001
Low exercise intensity (%)	23.8	54.9	<0.001	54.8	<0.001
Low exercise duration (%)	12.4	26.3	<0.001	22.7	0.013
Low exercise frequency (%)	13.8	33.0	<0.001	26.0	0.003

Data are mean ± SD, median (interquartile range), or %. P values were calculated from univariable Cox proportional hazards regression models with a new event (any-cause death/cardiovascular death) as outcome. AHT, antihypertensive medication; DBP, diastolic blood pressure; WHR, waist-to-hip ratio.

nurse. Blood pressure was measured twice after a 10-min rest with a 2-min interval, and the mean values were used in the analyses. Blood samples were drawn to determine and HbA_{1c}, serum creatinine, and lipid levels by routine methods as previously described (13).

LTPA was assessed by a self-report questionnaire, which comprised various items regarding exercise type, intensity, duration, and frequency. The details and validation of the questionnaire have been previously described (15–17) (Supplementary Table 1). The total amount of LTPA is reported in metabolic equivalents (MET-h/week), and patients were categorized as follows: sedentary (<10 MET-h/week), moderately active (10–40 MET-h/week), and active (>40 MET-h/week). We also analyzed other LTPA-related exposures: *1*) exercise intensity (low: no self-reported subjective shortness of breath and no sweating; moderate: a moderate degree of self-reported subjective shortness of breath and sweating; high: a high degree of subjective shortness of breath and sweating), *2*) single session duration (low: ≤30 min/session; moderate: 31–60 min/session; and high: >60 min/session), and *3*) exercise frequency (low: fewer than one session per week; moderate: one to two sessions per week; high: more than two sessions per week).

Statistical Analyses

Data were analyzed by using SPSS version 22.2 statistical software (IBM Corporation, Armonk, NY). Normally distributed continuous variables are expressed as mean ± SD; otherwise, data are expressed as median with interquartile range. Categorical variables are given as percentages. Between-group differences were assessed by using ANOVA for normally distributed variables and the Kruskal-Wallis test for nonnormally distributed variables. Categorical variables were analyzed by using the χ^2 test. The cumulative mortality was assessed by the Kaplan-Meier method, and the log-rank test was used to test between-group differences.

Follow-up started from the baseline visit, and the person-years at risk were calculated until death or the end of 2014. The association between the various LTPA components and mortality was analyzed by using univariable and multivariable Cox proportional hazards regression models. Because there was no interaction between the LTPA components and sex or diabetic nephropathy (defined as the presence of micro/macroalbuminuria or ESRD), all additional analyses were conducted by pooling all individuals together. The multivariable analyses first included the static confounders nephropathy status, sex, duration of diabetes, and age at onset of diabetes and then included in the final models the dynamic covariates HbA_{1c}, systolic blood pressure (SBP), triglycerides, smoking status, and BMI. In the subanalyses of patients with CKD, all CKD groups were analyzed together because the interaction term between the LTPA components and CKD groups was not significant. However, additional analyses were conducted to include CKD groups as a covariate. $P < 0.05$ was considered statistically significant.

RESULTS

This longitudinal study (mean follow-up time 11.4 ± 3.5 years) included 2,369 patients. At baseline, 310 patients had CKD, 48.5% were men, mean age was 40.1 ± 12.6 years, BMI 25.2 ± 3.6 kg/m^2, SBP 135 ± 19 mmHg, HbA_{1c} 8.3 ± 1.4%, and duration of diabetes 23.3 ± 12.8 years. At baseline, the median LTPA was 16.4 MET-h/week (5.3–32.9 MET-h/week), 44.8% of the patients had a history of former smoking (20.7%) or current smoking (24.1%), 68.9% had a normal UAER, and 6.5% had a cardiovascular disease event at baseline.

During follow-up, 270 deaths as a result of any cause occurred. Of these, 75 (27.8%) were cardiovascular deaths. Table 1 shows the baseline clinical characteristics of the patients who died as a result of any cause or cardiovascular events compared with those still alive during follow-up. The patients who died as a result of any cause were more often men, former or current smokers, older, heavier, and sedentary. These patients also had a higher SBP, longer duration of diabetes, more frequent use of antihypertensive drugs, worse lipid profile, and worse glycemic control. The baseline risk factors for a cardiovascular death were nearly identical to those for any cause, apart from the history of smoking that was not statistically significant for cardiovascular mortality.

Table 2 shows the 10-year cumulative all-cause mortality rates grouped by total amount of LTPA and its components' intensity, frequency, and exercise duration. In these univariable models, the total amount of LTPA and all the exercise components were associated with all-cause mortality during follow-up.

The multivariable Cox proportional hazards regression models are shown in Table 3. Comparisons were made for low and moderate versus high (the reference

Table 2—Ten-year cumulative incidence rates for all-cause mortality by LTPA and by exercise intensity, duration, and frequency

	Low*	Moderate*	High*	*P* value
LTPA				
Incidence	14.4 (12.2, 16.6)	6.6 (5.1, 8.1)	4.8 (2.7, 6.8)	<0.001
Participants (*n*)	833	1,109	427	
Events (*n*)	141	95	34	
Exercise intensity				
Incidence	17.7 (15.1, 20.2)	6.4 (5.1, 7.7)	2.3 (1.0, 3.6)	<0.001
Participants (*n*)	631	1,224	459	
Events (*n*)	141	101	15	
Exercise frequency				
Incidence	19.9 (16.5, 23.1)	6.6 (2.9, 10.2)	6.7 (5.6, 7.8)	<0.001
Participants (*n*)	375	158	1,813	
Events (*n*)	87	16	161	
Exercise duration				
Incidence	16.6 (12.9, 20.1)	6.6 (5.1, 8.1)	6.4 (4.7, 8.0)	<0.001
Participants (*n*)	300	1,149	726	
Events (*n*)	59	103	62	

Data are % (95% CI) unless otherwise indicated. *LTPA: low <10 MET-h/week; moderate 10–40 MET-h/week, and high >40 MET-h/week. Intensity: low (no self-reported subjective shortness of breath and no sweating), moderate (a moderate degree of self-reported subjective shortness of breath and sweating), and high (a high degree of subjective shortness of breath and sweating). Frequency: low fewer than one session/week, moderate one to two sessions/week, and high more than two sessions/week. Duration: low ≤30 min/session, moderate 31–60 min/session, and high >60 min/session.

Table 3—Cox proportional hazards regression models for low and moderate versus high total LTPA and exercise intensity, frequency, and duration for all-cause mortality

	Model 1	Model 2	Model 3
LTPA			
Low*	2.49 (1.71, 3.62)	2.07 (1.40, 3.06)	1.92 (1.29, 2.86)
Moderate*	1.11 (0.75, 1.64)	1.34 (0.89, 2.02)	1.37 (0.91, 2.07)
High*	1.00	1.00	1.00
Participants (*n*)	2,369	2,315	2,274
Events (*n*)	270	261	255
Exercise intensity			
Low	7.83 (4.60, 13.33)	2.78 (1.57, 4.90)	2.39 (1.34, 4.25)
Moderate	2.55 (1.48, 4.39)	1.42 (0.80, 2.50)	1.34 (0.76, 2.38)
High	1.00	1.00	1.00
Participants (*n*)	2,314	2,261	2,221
Events (*n*)	257	249	244
Exercise frequency			
Low	2.92 (2.25, 3.79)	2.35 (1.79, 3.09)	2.03 (1.53, 2.70)
Moderate	1.13 (0.68, 1.89)	1.45 (0.86, 2.43)	1.33 (0.79, 2.24)
High	1.00	1.00	1.00
Participants (*n*)	2,346	2,292	2,251
Events (*n*)	264	255	249
Exercise duration			
Low	2.50 (1.75, 3.57)	1.86 (1.29, 2.68)	1.79 (1.23, 2.58)
Moderate	1.08 (0.79, 1.48)	1.01 (0.73, 1.39)	1.09 (0.78, 1.51)
High	1.00	1.00	1.00
Participants (*n*)	2,175	2,126	2,092
Events (*n*)	224	217	214

Data are HR (95% CI) unless otherwise indicated. Model 1: exercise components and all-cause mortality. Model 2: model 1 plus sex, duration of diabetes, smoking status, age at onset of diabetes, and diabetic nephropathy. Model 3: model 2 plus SBP, triglycerides, BMI, and HbA_{1c}. *LTPA: low $<$10 MET-h/week; moderate 10–40 MET-h/week, and high $>$40 MET-h/week. Intensity: low (no self-reported subjective shortness of breath and no sweating), moderate (a moderate degree of self-reported subjective shortness of breath and sweating), and high (a high degree of subjective shortness of breath and sweating). Frequency: low fewer than one session/week, moderate one to two sessions/week, and high more than two sessions/week. Duration: low $\leq$30 min/session, moderate 31–60 min/session, and high $>$60 min/session.

group) for the amount of LTPA as well as its components with regard to all-cause mortality. Model 1 is a univariable model that included the exercise components and all-cause mortality. After adjustment for history of smoking and the static confounders sex, diabetic nephropathy, duration of diabetes, and age at onset of diabetes, all the exercise components were associated with all-cause mortality (model 2). In model 3, we added the dynamic risk factors of SBP, triglycerides, BMI, and HbA_{1c} that themselves could be affected by exercise. After this final adjustment, all exercise components were still associated with all-cause mortality.

The 10-year cumulative cardiovascular mortality rates are shown in Supplementary Table 2. The 10-year cumulative cardiovascular mortality rates were 4.7% (95% CI 3.2%, 6.2%) in the low, 1.9% (1.1%, 2.7%) in the moderate, and 1.8% (0.4%, 3.1%) in the high LTPA groups (P = 0.001). Similarly, the 10-year cumulative cardiovascular mortality rates were 6.7% (4.7%, 8.7%) in the low, 1.9% (1.1%, 2.7%) in the moderate, and 0.2% (0.0%, 0.6%) in the high exercise intensity groups ($P < 0.001$) and 5.5% (3.1%, 7.9%) in the low, 2.8% (0.1%, 5.4%) in the moderate, and 2.2% (1.4%, 3.0%) in the high exercise frequency groups (P = 0.01). The corresponding rates for exercise duration were 5.4% (2.6%, 8.0%) in the low, 2.0% (1.2%, 2.8%) in the moderate, and 2.7% (1.5%, 3.8%) in the high groups (P = 0.02).

Supplementary Table 3 shows the multivariable Cox proportional hazards regression models for all exercise components and cardiovascular mortality. After adding the static confounders and the history of smoking (model 2), exercise frequency and the intensity were still associated with cardiovascular mortality. However, after the final adjustment for all potential confounders (model 3), only exercise intensity was associated with cardiovascular mortality.

We repeated the multivariable analyses for men and women separately with respect to total amount of LTPA, its components, and all-cause mortality (Supplementary Tables 4 and 5). When adjusted for all confounders in model 3, both the total amount of LTPA and all the exercise components (frequency, duration, and intensity) were associated with all-cause mortality in men. In women, on the other hand, only exercise frequency and duration were associated with all-cause mortality in model 3.

Finally, we analyzed the relationship between LTPA and all-cause mortality in patients with CKD (n = 310). Of these patients, 127 died during follow-up as a result of any cause; 48.1% were men; and mean age was 48.8 $\pm$ 10.3 years, duration of diabetes 34.0 $\pm$ 9.9 years, BMI 26.0 $\pm$ 4.2 kg/m^2, SBP 146 $\pm$ 23 mmHg, and HbA_{1c} 8.4 $\pm$ 1.3%. Of the patients with CKD, 64 had received a kidney transplant, and 36 were undergoing dialysis. Table 4 presents the Cox proportional hazards regression models for this population by LTPA, its components, and all-cause mortality. In the univariable model (model 1), all exercise components were associated with all-cause mortality, and this association remained significant in model 2 when adjusted for the static risk factors and history of smoking. In model 3, however, when adjusted for the dynamic confounders, only the total amount of LTPA and exercise frequency were independently associated with all-cause mortality. Additional analyses that included CKD groups as a covariate did not change the results. Only the effect of duration of exercise on mortality became borderline significant (P = 0.06) in model 2. When eGFR was included as a covariate in the final Cox proportional hazards regression model, the association between exercise frequency and mortality remained significant (P = 0.045), but the total amount of LTPA did not. We repeated the same regression analyses in the patients without CKD, and the results were no different from the entire group of patients with type 1 diabetes; that is, the total amount of LTPA and the all exercise components were associated with all-cause mortality when adjusted for all the previous confounders (data not shown). Separate additional Cox proportional hazards regression models in patients undergoing dialysis or patients who had received a kidney transplant are shown in Supplementary Tables 6 and 7.

Table 4—Cox proportional hazards regression models for low versus moderate/high* total LTPA and exercise intensity, frequency, and duration for all-cause mortality in patients with type 1 diabetes and CKD

	Model 1	Model 2	Model 3
LTPA			
Mortality	1.89 (1.33, 2.69)	1.72 (1.20, 2.46)	1.47 (1.02, 2.12)
Participants (*n*)	310	303	296
Events (*n*)	127	124	119
Exercise intensity			
Mortality	2.10 (1.45, 3.03)	1.80 (1.23, 2.64)	1.39 (0.92, 2.09)
Participants (*n*)	297	291	285
Events (*n*)	119	117	113
Exercise frequency			
Mortality	2.39 (1.65, 3.46)	2.20 (1.48, 3.26)	1.90 (1.26, 2.87)
Participants (*n*)	306	299	292
Events (*n*)	124	121	116
Exercise duration			
Mortality	1.93 (1.24, 3.01)	1.69 (1.07, 2.67)	1.49 (0.92, 2.42)
Participants (*n*)	264	259	256
Events (*n*)	99	97	95

Data are HR (95% CI) unless otherwise indicated. Model 1: exercise components and all-cause mortality. Model 2: model 1 plus sex, duration of diabetes, smoking status, age at onset of diabetes, and diabetic nephropathy. Model 3: model 2 plus SBP, triglycerides, BMI, and HbA_{1c}. *LTPA: low $<$10 MET-h/week; moderate 10–40 MET-h/week; and high $>$40 MET-h/week. Intensity: low (no self-reported subjective shortness of breath and no sweating), moderate (a moderate degree of self-reported subjective shortness of breath and sweating), and high (a high degree of subjective shortness of breath and sweating). Frequency: low fewer than one session/week, moderate one to two sessions/week, and high more than two sessions/week. Duration: low $\leq$30 min/session, moderate 31–60 min/session, and high $>$60 min/session.

CONCLUSIONS

In this prospective study, we show that baseline LTPA is associated with reduced all-cause mortality in type 1 diabetes. Of note, physical activity is associated with a lower risk of premature mortality in patients with type 1 diabetes and CKD. In addition, we show that all exercise components are associated with reduced mortality rates during follow-up. This finding is unaffected by any adjustment for potential confounders.

The observation that physical activity reduces mortality in patients with CKD is novel, and to our knowledge, no other studies have investigated the effect of exercise on mortality in this patient group. The finding is not unexpected given that we previously showed that exercise, and in particular intensive exercise, is associated with a reduced risk of progression of diabetic nephropathy in individuals with type 1 diabetes (3). Patients with CKD are expected to be more physically inactive and to have a lower level of fitness and muscle function (9–12), but exercise appears to be safe and to have significant health benefits in these patients, and 30 min of daily moderate-intensity exercise is therefore recommended (9). In the current study, total LTPA as well as all its components were associated with all-cause mortality when adjusted for smoking and static risk factors. However, when the dynamic confounders were added to the Cox proportional hazards regression model, only the total amount of LTPA and a higher exercise frequency were associated with a reduced mortality rate. These findings support the current recommendations for CKD management and suggest that exercise should always be a part of the treatment regimen.

With respect to exercise and mortality in individuals with type 1 diabetes, only a few previous longitudinal studies have been performed. The Pittsburgh IDDM Morbidity and Mortality Study showed that sedentary men were more likely to die during follow-up than active men, also after controlling for potential confounders such as age, BMI, insulin dose, presence of diabetic complications, cigarette smoking, and current alcohol drinking (7). Of note, participation in team sports during high school or college was associated with a reduced mortality risk in men, although this association was no more significant after controlling for other potential confounders such as age and year of type 1 diabetes onset, smoking status, alcohol consumption, hypertension, renal disease, and education level (6). The EURODIAB Prospective Complications Study showed an inverse association between moderate or vigorous physical activity once or more a week at baseline and all-cause mortality in both sexes. However, this association was reduced to a nonsignificant level after adjustment for potential confounders (8).

The current finding of an association between exercise and all-cause mortality in the entire study cohort not only is in line with but also extends the observations from the EURODIAB Prospective Complications Study and the Pittsburgh IDDM Morbidity and Mortality Study (6,8). We also observed that the association is true for both sexes with respect to duration and frequency, but the associations with total amount of LTPA and intensity were significant only in men after adjustment for confounders. However, on the basis of previous studies and the current study, sex-specific differences regarding the association between baseline physical activity and all-cause mortality are unlikely.

The data regarding the effect of physical activity on cardiovascular mortality are in line with the data for all-cause mortality, although after adjustment for all potential confounders, only exercise intensity remained associated with cardiovascular mortality. This finding probably is due to lost power because the number of cardiovascular deaths was only 75 compared with 270 deaths as a result of any cause. We have previously shown that exercise, and particularly intensive and frequent exercise, is associated with a reduced risk of incident cardiovascular events in type 1 diabetes (4). Moreover, higher exercise intensity was associated with lower risk of diabetic nephropathy, a main driver of the risk of cardiovascular disease (3). Given that cardiovascular disease is the most common cause of death among patients with type 1 diabetes (18), that exercise intensity also is associated with a lower risk of cardiovascular mortality is not surprising. The reason why only intensity remains significant after adjustment for dynamic confounders is not known, but it can be hypothesized that exercise intensity is the most important component of LTPA because of its impact on heart rate and autonomic nervous function. We have previously shown that patients with type 1 diabetes display reduced baroreflex sensitivity (19), which is clinically detectable as a higher pulse rate and, thus, potentially reduced exercise

tolerance and fitness. Another possibility is that the dynamic confounders are themselves affected by exercise.

The major strengths of this study are the substantially larger nationwide study cohort compared with previous studies and the prospective design. Furthermore, the LTPA questionnaire has been previously validated in the Finnish population and is custommade for Finnish conditions (17). An important feature of the study compared with previous longitudinal studies is that we were able to analyze not only the total amount of LTPA but also its main components. Furthermore, to our knowledge, no prospective data are available in the literature about exercise and mortality in patients with type 1 diabetes and CKD. Finally, the mortality data are complete, and no patients were lost to follow-up.

The study also has some limitations. Exercise was self-reported, and because work-related exercise was not assessed, some overestimation or underestimation of the true activity level of the patients exists. The ideal method to assess physical activity would be to use more accurate objective measurements, such as pedometers or accelerometers (20), but although such methods are feasible for smaller study populations, they are difficult to apply to nationwide cohorts, such as ours. Exercise was assessed only at baseline, and change of exercise habits over time, therefore, was not evaluated. On the other hand, the questionnaire has been shown to be representative and to have a small intraindividual variability (15–17). Unfortunately, we were not able to evaluate the interaction between exercise and other lifestyle factors, such as nutrition or socioeconomic status, in the current study.

In conclusion, the findings indicate that physical activity is associated with reduced all-cause and cardiovascular mortality in patients with type 1 diabetes. In addition, we show an association between physical activity and reduced all-cause mortality in patients with type 1 diabetes and CKD. Thus, exercise can be recommended to all patients with type 1 diabetes, including those with CKD.

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Author Contributions. H.T.-D. and V.H. analyzed the data. H.T.-D. and P.-H.G. drafted the manuscript. J.W., C.F., L.M.T., M.S., N.E., H.O.T., and P.-H.G. were involved in data collection. All authors contributed to and approved of the final submitted version of the manuscript. P.-H.G. 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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