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Association of Cycling With All-Cause and Cardiovascular Disease Mortality Among Persons With Diabetes

The European Prospective Investigation Into Cancer and Nutrition (EPIC) Study

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IMPORTANCE Premature death from all causes and cardiovascular disease (CVD) causes is higher among persons with diabetes.

OBJECTIVE To investigate the association between time spent cycling and all-cause and CVD mortality among persons with diabetes, as well as to evaluate the association between change in time spent cycling and risk of all-cause and CVD mortality.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study included 7459 adults with diabetes from the European Prospective Investigation into Cancer and Nutrition study. Questionnaires regarding medical history, sociodemographic, and lifestyle information were administered in 10 Western European countries from 1992 through 2000 (baseline examination) and at a second examination 5 years after baseline. A total of 5423 participants with diabetes completed both examinations. The final updated primary analysis was conducted on November 13, 2020.

EXPOSURES The primary exposure was self-reported time spent cycling per week at the baseline examination. The secondary exposure was change in cycling status from baseline to the second examination.

MAIN OUTCOMES AND MEASURES The primary and secondary outcomes were all-cause and CVD mortality, respectively, adjusted for other physical activity modalities, diabetes duration, and sociodemographic and lifestyle factors.

RESULTS Of the 7459 adults with diabetes included in the analysis, the mean (SD) age was 55.9 (7.7) years, and 3924 (52.6%) were female. During 110 944 person-years of follow-up, 1673 deaths from all causes were registered. Compared with the reference group of people who reported no cycling at baseline (0 min/wk), the multivariable-adjusted hazard ratios for all-cause mortality were 0.78 (95% CI, 0.61-0.99), 0.76 (95% CI, 0.65-0.88), 0.68 (95% CI, 0.57-0.82), and 0.76 (95% CI, 0.63-0.91) for cycling 1 to 59, 60 to 149, 150 to 299, and 300 or more min/wk, respectively. In an analysis of change in time spent cycling with 57 802 person-years of follow-up, a total of 975 deaths from all causes were recorded. Compared with people who reported no cycling at both examinations, the multivariable-adjusted hazard ratios for all-cause mortality were 0.90 (95% CI, 0.71-1.14) in those who cycled and then stopped, 0.65 (95% CI, 0.46-0.92) in initial noncyclists who started cycling, and 0.65 (95% CI, 0.53-0.80) for people who reported cycling at both examinations. Similar results were observed for CVD mortality.

CONCLUSION AND RELEVANCE In this cohort study, cycling was associated with lower all-cause and CVD mortality risk among people with diabetes independent of practicing other types of physical activity. Participants who took up cycling between the baseline and second examination had a considerably lower risk of both all-cause and CVD mortality compared with consistent noncyclists.

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Supplemental content

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Premature death from all causes and cardiovascular disease (CVD) is higher among people with diabetes.[1] Regular physical activity is a critical behavioral target in the management of diabetes,[2] but only structured exercise, in contrast with advice only, has been shown to improve CVD risk factors.[3-6] Thus, it is necessary to investigate the influence of engagement in specific unstructured physical activities on mortality in this patient population.

Cohort studies in populations with diabetes have reported inverse associations between overall physical activity, leisure-time physical activity (LTPA), and walking with all-cause and CVD mortality.[7,8] However, associations with walking have been inconsistent, likely because only moderate-intensity walking appears to be associated with a reduced risk of all-cause and CVD mortality.[9] Meeting the physical activity recommendations both in terms of total physical activity volume as well as intensity is a major challenge, especially in people with diabetes.[10-12] Because lack of time is often quoted as a barrier, incorporating activities into everyday life may be an effective strategy. Cycling is a potential activity to replace motorized transport for short-to-medium distance trips (eg, during commuting to work without a substantial effect on time use). As moderate-to-high intensities are reached during cycling at self-selected paces in adults,[13-16] cycling could decrease the risk of premature mortality. It may also be a feasible strategy because cycling is one of the preferred activities in people with type 2 diabetes.[17,18] It is well established that there is a strong inverse association between cycling and the risk of all-cause and cause-specific mortality, such as CVD, in the general population.[19-21] However, to our knowledge, there are no studies that have examined the role of cycling in preventing premature mortality in people with diabetes.

The primary aim of this cohort study was to investigate the associations between cycling and all-cause and CVD mortality among persons with diabetes. A secondary aim was to study the associations between change in cycling over a 5-year period and all-cause and CVD mortality.

Key Points

Question Is cycling associated with risk of all-cause and cardiovascular disease mortality among persons with diabetes?

Findings In this cohort study of 7459 persons with diabetes, cycling was associated with at least a 24% lower all-cause mortality rate when compared with noncyclists, independent of other physical activity and putative confounders. Taking up cycling over a 5-year period was associated with at least a 35% lower risk of all-cause mortality when compared with consistent noncyclists.

Meaning Cycling could be encouraged as an activity for persons with diabetes to lower the risk of premature mortality.

Methods

Study Design and Setting

This study was a prospective cohort study of people with diabetes at baseline in the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohort.[22] In EPIC, 23 centers in 10 Western European countries (France, Italy, Spain, United Kingdom, the Netherlands, Greece, Germany, Sweden, Denmark, and Norway) collected information on nutrition, lifestyle, anthropometry, and medical history from more than 521 234 participating men and women.[22] Medical history, sociodemographic, and lifestyle information was assessed by questionnaires at baseline between 1992 and 1998 (baseline examination) and at a second examination between 1996 and 2011. Data were only available from 22 centers because data from Greece were not released for this study. The ethical review boards from the International Agency for Research on Cancer and all local participating centers approved this study. Informed consent was obtained from all participants.

Study Population

From the entire EPIC population, people with diabetes at the baseline assessment were included in the present study. Diabetes was based on self-report on a single occasion or by a second source (at least 1), including repeated self-report, by a general physician, linkage to register or medical record at a later point, prescription of use of glucose-lowering or diabetes-related medication, or baseline glycated hemoglobin at least 6.0% (42 mmol/mol [to convert to proportion of total hemoglobin, multiply by 0.01]).[7]

Data Collection

Study procedures have been described in detail elsewhere.[22] Briefly, height, weight, and waist circumference were measured using similar protocols across study centers.[22] Body mass index was calculated as weight in kilograms divided by height in meters squared. Central obesity was defined according the International Diabetes Federation criteria.[23] Diabetes duration was calculated as the time from self-reported age or calendar year of medical diagnosis to baseline.

Dietary intake, including alcohol consumption, was assessed by a questionnaire (quantitative, semiquantitative, or a combination) and 7-day or 14-day record, and individual energy and nutrient intake was based on the standardized EPIC nutrient database.[22,24] Because the Mediterranean diet is associated with improved metabolic control and decreased risk of diabetes,[25-27] it was included as a covariate expressed as the relative Mediterranean diet score.[25,27,28] Dietary data were only available for the baseline examination.

Assessment of Physical Activity

Information about physical activity habits was obtained from a lifestyle questionnaire and included information about duration and frequency of leisure-time and occupational physical activity.[22,29] Weekly time spent cycling to and/or from work and leisure time during winter and summer was averaged into a single variable of total annual cycling time and then categorized as 0, 1 to 59, 60 to 149, 150 to 299, and 300 or more min/wk. Change in total cycling from baseline to the second examination was categorized based on total time spent cycling at the 2 examinations: (1) noncycling: participants who reported zero minutes of cycling at both examinations; (2) stopped cycling: participants who reported cycling (any amount) at baseline but not at the second examination; (3)

started cycling: participants who did not report cycling at baseline but did report cycling (any amount) at the second examination; or (4) maintained cycling: those who were consistent cyclists at both examinations.

The LTPA energy expenditure (without cycling included) metabolic equivalent of tasks in hours per week (MET-h/wk[15]) was calculated at both examinations as the sum of energy expenditures from the following activities: gardening, do-it-yourself activities, stair climbing, housework activities, walking, and sports. Because information on stair climbing was only available from 4 study centers at the second examination, this activity was not included in the second examination LTPA variable. Occupational physical activity was reported in categories of sedentary occupation, standing occupation, manual or heavy manual work, or nonworker.[29]

Outcome Ascertainment

The primary and secondary outcomes were all-cause and CVD mortality, respectively. Any deaths due to CVD were coded according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, using the codes I00 to I99. Vital status and cause of death were obtained through record linkage with registries, physicians or hospitals, or direct follow-up.[30] Follow-up end for the primary and secondary analyses was on March 26, 2015 (eTable 1 in Supplement 1).

Statistical Analysis

A statistical analysis plan was developed (Supplement 2) and preregistered (NCT04171557) prior to commencing the analyses. The risks of all-cause and CVD mortality were computed as hazard ratios (HRs) with 95% CIs according to weekly time spent cycling at baseline estimated using stratified Cox proportional hazard regression models with age as the underlying time scale. Analyses were corrected for delayed entry. Participants were considered at risk from age at baseline examination in the primary analyses and from age at the second examination in the analyses of change in cycling. Participants leaving the study during follow-up owing to emigration or premature withdrawal were right censored at the age of emigration or withdrawal. A priori, participants with sufficient information to be included in the most extensive statistical models (models 3 and 2 for the primary and secondary analyses, respectively) were included in the primary models (models 2 and 1 for the primary and secondary analyses, respectively).

A crude model (model 1) was fitted with categories of cycling as exposure (0 [reference], 1-59, 60-149, 150-299, and ≥300 min/wk), adjusted for sex and age (years), and further stratified by study center to adjust for confounding of this variable. The proportional hazards assumption for cycling was met within each stratum. Model 1 was further adjusted for attained educational level (no formal education, primary school, technical or professional school, secondary school, or university degree), smoking status (never smoker, former smoker, or current smoker), diabetes duration (years), adherence to the Mediterranean diet (relative Mediterranean diet score: low, 0-6 points; medium, 7-10 points; or high, 11-18 points),[25,27] total energy intake (quartiles of kcal/d),[24] physical activity excluding cycling (quartiles of LTPA energy expenditure), and occupational physical activity (sedentary occupation, standing occupation, manual or heavy manual work, nonworker, or unknown status) (model 2 [main model]). Finally, history of prevalent stroke (yes or no), previous myocardial infarction (yes or no), prevalent cancer (yes or no), hypertension (yes or no), hyperlipidemia (yes or no), and central obesity (yes or no) at baseline were added as covariates (model 3). Effect modification by sex and diabetes duration (≥5 vs <5 years) was evaluated statistically using the likelihood-ratio test by comparing model 2, adding a multiplicative interaction term for sex or diabetes duration and cycling with a model including only main effects. Because several covariates did not meet the proportional hazard assumption in the multivariable models 2 and 3, we computed an extended Cox regression analysis in which we stratified by study center and energy intake in the analyses with all-cause mortality as the outcome. In the models with CVD mortality as the outcome, we stratified by study center, educational level, and LTPA (excluding cycling). We conducted a range of preplanned sensitivity analyses for the primary model (model 2) specified in the statistical analysis plan (Supplement 2) to investigate the association of residual confounding and reverse causality (excluding all deaths and CVD deaths within the first 2 years following the baseline examination).

In the preplanned secondary analysis, associations between all-cause and CVD mortality and change in cycling (from baseline to second examination) were investigated. The associations were initially adjusted for sex and age at the second examination and stratified by study center. A multivariable model was fitted additionally adjusting for educational level at baseline, smoking status at both examinations, diabetes duration at the time of second examination, LTPA (excluding cycling) at both examinations, and occupational physical activity at the second examination. The multivariable analyses were stratified by study center, baseline occupational physical activity, adherence to the relative Mediterranean diet, and total energy intake at baseline.

Because the associations between baseline and cycling and all-cause or CVD mortality were nonlinear, we computed (post hoc) restricted cubic splines of the respective associations with knot placements at the 10th, 50th, and 90th percentiles, as recommended by Harrell.[31] These analyses were repeated using the average of baseline and second examinations. Because of large amounts of zero values in the cycling variable, the percentiles were computed excluding zero. Moreover, 10-year adjusted (standardized) cumulative mortality according to cycling at baseline or change in cycling status, consistent with the primary models, were estimated post hoc. Flexible parametric survival models[32] with additional postestimation of adjusted differences (95% CIs) in 10-year cumulative mortality comparing 0 min/wk of cycling at baseline and/or at the second examination to higher levels of cycling or stopping/starting/maintaining cycling were used. Also, to assess the influence of unmeasured confounding, the E-value was calculated based on our estimated HR for all-cause and CVD mortality.[33] All analyses were conducted using STATA IC,

version 16.1 (StataCorp), with 2-sided α = .05 considered statistically significant.

Results

Of the 492 763 participants enrolled in the EPIC cohort, 10 995 had diabetes at the baseline examination. The analytic sample consisted of 7459 participants, of whom 4701 (63.0%) had confirmed diabetes and 4699 (63.0%) were noncyclists. Among the sample, the mean (SD) age was 55.9 (7.7) years, the mean (SD) diabetes duration was 7.7 (8.1) years, and 3924 (52.6%) were female (**Table 1**). The main reason for exclusion from the analytic sample was missing covariate or exposure information (eFigure 1 in Supplement 1). Reasons for missing data are reported in eTable 2 in Supplement 1.

The participants were followed for a mean (SD) of 14.9 (4.4) years (110 944 person-years) with 1673 deaths from all causes and 811 deaths attributable to CVD. A subset of participants (n = 5423) also completed the second examination and were included in the analysis of change in cycling. This analysis had a mean (SD) of 10.7 (4.3) years of follow-up, accumulating a total of 57 802 person-years with 975 deaths from all causes and 429 from CVD.

Baseline Cycling and All-Cause and CVD Mortality

The HR for all-cause mortality was lower for people reporting any cycling (>0 min/wk) when compared with noncyclists (model 1; **Table 2**[34]). Cycling was also associated with a reduced risk of CVD mortality (Table 2). Adjusting for educational level, lifestyle risk factors, and diabetes duration did not materially change the association between cycling and all-cause mortality (model 2; Table 2). The 10-year cumulative mortality risk difference relative to 0 min/wk of cycling for ascending cycling categories (1-59, 60-149, 150-299, and ≥300 min/wk) were −1.9%, −2.0%, −2.7%, and −2.1% for all-cause mortality and −1.2%, −1.2%, −2.2%, and −1.0% for CVD mortality, respectively (eTable 3 in Supplement 1), with the lowest category of cycling consistently having the highest cumulative mortality (eFigure 2 in Supplement 1).

No statistically significant multiplicative interactions of sex or diabetes duration and cycling were observed for all-cause nor CVD mortality (eTable 4 in Supplement 1). Further adjustment for existing conditions and CVD risk factors only slightly attenuated the associations (model 3; Table 2). Sensitivity analyses investigating residual confounding by smoking, sports participation, self-reported diabetes, and reverse causality broadly confirmed the associations between cycling and both all-cause and CVD mortality (eTable 5 in Supplement 1), and E-values ranged from 1.66 to 2.91 in categories of baseline cycling (eTable 6 in Supplement 1).

The dose-response relationship with baseline cycling as a continuous variable for both all-cause and CVD mortality was modeled post hoc; for comparison, the association for LTPA (excluding cycling) is provided (**Figure 1**[34]). This revealed a reversed J-shaped association between both outcomes and cycling, and a linear association for LTPA (excluding cycling) (HRs per 10 MET-h increase per week: 0.97 [95% CI, 0.95-0.98] and 0.96 [95% CI, 0.94-0.98] for all-cause and CVD mortality, respectively) (Figure 1). The distribution of cycling and LTPA among observations with and without events underlying these analyses are found in eFigure 3 in Supplement 1. The associations between average cycling at baseline and second examination approximated a curve-linear dose-response relationship (eFigure 4 and eTables 7 and 8 in Supplement 1).

Change in Cycling and All-Cause and CVD Mortality

For both all-cause and CVD mortality, HRs were 0.65 or less among participants who started or maintained cycling (**Figure 2**) relative to noncyclists (risk differences relative to noncyclists were −3.7% for all-cause mortality and −2.7% for CVD mortality; eTable 9 and eFigure 5 in Supplement 1). After excluding deaths within the first 2 years from the second examination, the associations were unchanged: HRs for all-cause mortality were 0.93 (95% CI, 0.72-1.19), 0.66 (95% CI, 0.45-0.95), and 0.64 (95% CI, 0.51-0.80) for people who stopped, started, or maintained cycling, respectively, compared with noncyclists), and corresponding HRs for CVD mortality were 1.08 (95% CI, 0.77-1.51), 0.56 (95% CI, 0.31-0.99), and 0.54 (95% CI, 0.39-0.75). E-values were more than 2 for the groups that started cycling and maintained cycling (eTable 6 in Supplement 1).

Discussion

We observed that time spent cycling was associated with a lower risk of all-cause and CVD mortality in people with diabetes, independent of other physical activities and other putative confounders. However, the dose-response relationships were ambiguous.

The association between cycling and all-cause and CVD mortality in this study of person with diabetes was of the same magnitude and direction as observed in the healthy population.[13,20,21,35-41] This is moreover in line with previous observations by Andersen et al,[8] who observed that the associations between physical activity and all-cause mortality seemed to be similar between the healthy population and persons living with chronic disease, including cardiovascular, lung, and musculoskeletal diseases. However, their investigation did not include persons with diabetes nor did it specifically investigate the interaction between chronic disease state and associations between cycling and all-cause mortality.[8] The lower risk of all-cause and CVD mortality associated with overall physical activity as well as walking among persons with diabetes is well established.[7,9,42-48] The present investigation extends the level of evidence within this field by documenting that cycling and taking up cycling may offer specific health benefits in people with diabetes over and above other physical activities, including walking. Mixed-mode commuting (walking and/or cycling) has been associated with decreased mortality in persons with diabetes.[49] However, the association was weaker as compared with our observations. Because physical activity intensity is important in mediating the health benefits from walking among people with type 2 diabetes,[9,50] a lower intensity of physical activity, such as walking, when

Table 1. Baseline Characteristics of Sample Subgroups and the Total Cohort

Characteristic	Participants, No. (%)					
	Time spent cycling at first examination, min/wk					
	0	1-59	60-149	150-299	≥300	Total
Participants	4648	422	999	736	654	7459
Annual cycling, median (IQR), min/wk	0 (0-0)	30 (30-30)	90 (60-120)	180 (165-240)	420 (330-600)	0 (0-90)
Sex						
Male	1972 (42.4)	251 (59.5)	561 (56.2)	401 (54.5)	350 (53.5)	3535 (47.4)
Female	2676 (57.6)	171 (40.5)	438 (43.8)	335 (45.5)	304 (46.5)	3924 (52.6)
Age, mean (SD), y	55.6 (7.8)	55.0 (7.4)	56.0 (7.9)	56.4 (7.1)	57.3 (6.9)	55.9 (7.7)
Diabetes duration, mean (SD), y	7.7 (8.1)	7.3 (7.4)	7.7 (8.4)	7.7 (8.1)	7.5 (8.0)	7.7 (8.1)
Educational level						
None	1086 (23.4)	6 (1.4)	42 (4.2)	27 (3.7)	18 (2.8)	1179 (15.8)
Primary school	1642 (35.3)	179 (42.4)	354 (35.4)	295 (40.1)	287 (43.9)	2757 (37.0)
Technical/professional school	793 (17.1)	98 (23.2)	277 (27.7)	210 (28.5)	193 (29.5)	1571 (21.1)
Secondary school	390 (8.4)	43 (10.2)	107 (10.7)	66 (9.0)	58 (8.9)	664 (8.9)
University degree	737 (15.9)	96 (22.7)	219 (21.9)	138 (18.8)	98 (15.0)	1288 (17.3)
Smoking status						
Never	2363 (50.8)	161 (38.2)	400 (40.0)	304 (41.3)	251 (38.4)	2757 (46.6)
Former	1243 (26.7)	164 (38.9)	373 (37.3)	272 (37.0)	268 (41.0)	1571 (31.1)
Current	1042 (22.4)	97 (23.0)	226 (22.6)	160 (21.7)	135 (20.6)	664 (22.3)
BMI,[a] mean (SD)	29.4 (5.1)	28.0 (4.5)	28.2 (4.8)	28.6 (4.6)	28.6 (4.7)	29.0 (5.0)
Waist circumference, mean (SD), cm[b]						
Male	101.4 (11.3)	98.8 (10.7)	98.9 (10.8)	99.1 (10.1)	99.3 (11.2)	100.4 (11.1)
Female	92.2 (13.0)	86.7 (12.5)	89.5 (13.5)	92.0 (13.6)	91.6 (12.9)	91.6 (13.1)
Central obesity						
Yes	3681 (79.2)	280 (66.4)	707 (70.8)	558 (75.8)	487 (74.5)	5713 (76.6)
No	967 (20.8)	142 (33.6)	292 (29.2)	178 (24.2)	167 (25.5)	1746 (23.4)
LTPA (excluding cycling), median (IQR), MET-h/wk						
Gardening	0.0 (0.0-8.0)	4.0 (0.0-10.0)	4.0 (0.0-14.0)	4.0 (0.0-14.0)	4.0 (0.0-16.0)	0.0 (0.0-11.0)
Do-it-yourself activities	0.0 (0.0-4.5)	4.5 (0.0-13.5)	4.5 (0.0-9.0)	2.3 (0.0-9.0)	0.0 (0.0-13.5)	0.0 (0.0-6.8)
Stair climbing	0.9 (0.0-2.1)	1.0 (0.4-2.6)	1.3 (0.4-2.6)	1.3 (0.3-2.6)	1.3 (0.4-2.6)	1.0 (0.3-2.3)
Housework	30.0 (3.0-84.0)	12.0 (0.0-42.0)	12.0 (6.0-42.0)	15.0 (6.0-45.0)	21.0 (6.0-45.0)	21.0 (3.0-63.0)
Walking	15.0 (6.0-27.0)	10.5 (4.5-21.0)	12.0 (6.0-21.0)	15.0 (9.0-27.0)	21.0 (12.0-36.0)	15.0 (6.0-27.0)
Sports	0.0 (0.0-0.0)	0.0 (0.0-6.0)	0.0 (0.0-9.0)	0.0 (0.0-11.3)	0.0 (0.0-12.0)	0.0 (0.0-6.0)
Occupational physical activity						
Sedentary occupation	993 (21.4)	121 (28.7)	258 (25.8)	172 (23.4)	119 (18.2)	1663 (22.3)
Standing occupation	964 (20.7)	80 (19.0)	179 (17.9)	137 (18.6)	110 (16.8)	1470 (19.7)
Manual work	433 (9.3)	49 (11.6)	112 (11.2)	84 (11.4)	69 (10.6)	747 (10.0)
Nonworker	2204 (47.4)	169 (40.0)	442 (44.2)	331 (45.0)	336 (51.4)	3482 (46.7)
Unknown	54 (1.2)	3 (0.7)	8 (0.8)	12 (1.6)	20 (3.1)	97 (1.3)
Energy intake, mean (SD), kcal/d	2025.1 (640.5)	2154.6 (641.9)	2103.0 (631.9)	2072.6 (640.9)	2120.9 (664.6)	2056.0 (642.9)
Adherence to relative Mediterranean diet						
Low	772 (16.6)	89 (21.1)	301 (30.1)	212 (28.8)	203 (31.0)	1577 (21.1)
Medium	2007 (43.2)	231 (54.7)	499 (49.9)	378 (51.4)	312 (47.7)	3427 (45.9)
High	1869 (40.2)	102 (24.2)	199 (19.9)	146 (19.8)	139 (21.3)	2455 (32.9)
Comorbidities						
Prevalent cancer	204 (4.4)	17 (4.0)	38 (3.8)	34 (4.6)	35 (5.4)	328 (4.4)
Prevalent stroke	156 (3.4)	11 (2.6)	36 (3.6)	17 (2.3)	16 (2.4)	236 (3.2)
Myocardial infarction	225 (4.8)	23 (5.5)	56 (5.6)	38 (5.2)	35 (5.4)	377 (5.1)
Hyperlipidemia	1943 (41.8)	194 (46.0)	361 (36.1)	278 (37.8)	252 (38.5)	3028 (40.6)
Hypertension	2200 (47.3)	203 (48.1)	485 (48.5)	359 (48.8)	348 (53.2)	3595 (48.2)

Abbreviations: BMI, body mass index; IQR, interquartile range; LTPA, leisure-time physical activity; MET-h/wk, metabolic equivalent of tasks in hours per week.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] To convert centimeters to inches, divide by 0.39.

Table 2. Association Between Total Volume of Cycling at the Baseline Examination and All-Cause and CVD Mortality

	Cycling at first examination, HR (95% CI), min/wk				
Variable	0	1-59	60-149	150-299	≥300
MET-h[a]	0	0.1-7.4	7.5-18.6	18.7-37.4	≥37.5
Participants, No.	4648	422	999	736	654
Total person-years	70 741	5994	14 395	10 521	9292
Cases of all-cause mortality	1059	79	231	150	154
Mortality rate/1000 person-years	14.97 (14.10-15.90)	13.18 (10.57-16.43)	16.04 (14.11-18.25)	14.26 (12.15-16.37)	16.57 (14.15-19.14)
Model 1[b]	1 [Reference]	0.76 (0.60-0.96)	0.72 (0.62-0.84)	0.65 (0.55-0.78)	0.71 (0.60-0.85)
Model 2[c]	1 [Reference]	0.78 (0.61-0.99)	0.76 (0.65-0.88)	0.68 (0.57-0.82)	0.76 (0.63-0.91)
Model 3[d]	1 [Reference]	0.81 (0.64-1.03)	0.77 (0.66-0.90)	0.70 (0.59-0.84)	0.81 (0.68-0.97)
Cases of CVD mortality	499	41	119	66	86
Mortality rate/1000 person-years	7.05 (6.46-7.70)	6.84 (5.04-9.29)	8.27 (6.91-9.89)	6.27 (4.93-7.89)	9.26 (7.49-11.43)
Model 1[b]	1 [Reference]	0.72 (0.52-1.00)	0.72 (0.59-0.89)	0.55 (0.42-0.71)	0.75 (0.59-0.96)
Model 2[e]	1 [Reference]	0.79 (0.56-1.11)	0.75 (0.60-0.93)	0.57 (0.44-0.76)	0.80 (0.62-1.03)
Model 3[f]	1 [Reference]	0.83 (0.59-1.18)	0.78 (0.63-0.98)	0.61 (0.46-0.81)	0.91 (0.70-1.17)

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; LTPA, leisure-time physical activity; MET-h, metabolic equivalent of tasks in hours.

[a] The MET-h is calculated based on the Compendium of Physical Activities using the code 01015 "Bicycling, general" with an estimated intensity of 7.5 MET-h.[34] To convert minutes of cycling to MET-h, divide by 60 and multiply by 7.5. Exposure variables were obtained at the baseline examination.

[b] Stratified according to study center and adjusted for sex and age.

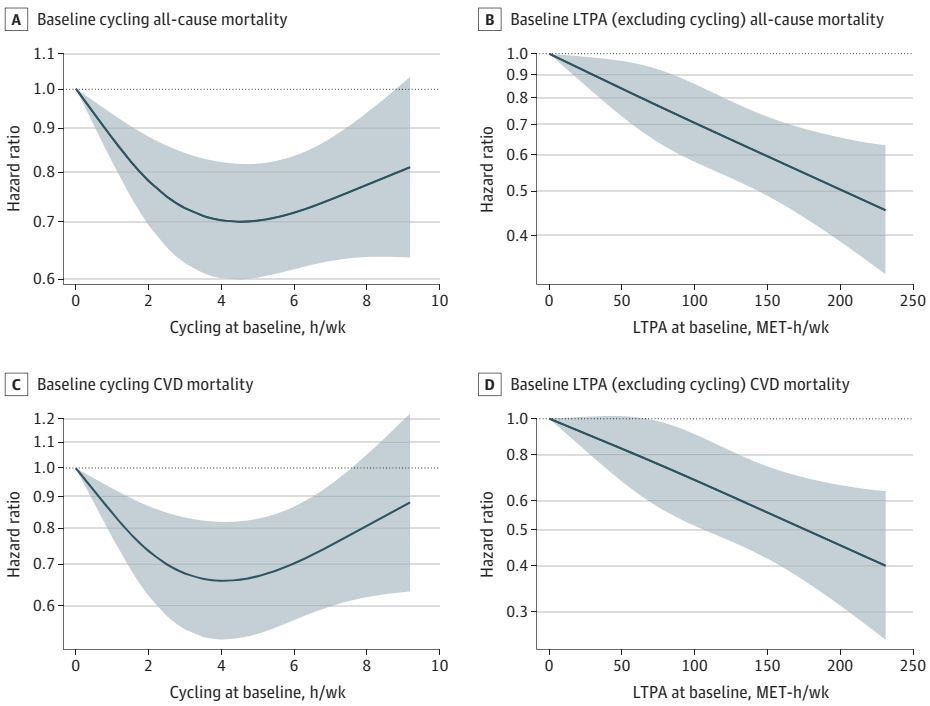
[c] Stratified according to study center and total energy intake (quartiles of kcal/wk). Adjusted for sex, age, educational level, smoking status, diabetes duration, adherence to the Mediterranean diet, LTPA (excluding cycling), and occupational physical activity.

[d] Stratified according to study center and total energy intake (quartiles of kcal/wk). Adjusted for sex, age, educational level, smoking status, diabetes duration, adherence to the Mediterranean diet, LTPA (excluding cycling), occupational physical activity, prevalent stroke, myocardial infarction, prevalent cancer, hyperlipidemia, hypertension, and central obesity.

[e] Stratified according to study center, educational level, and LTPA (excluding cycling). Adjusted for sex, age, smoking status, diabetes duration, adherence to the Mediterranean diet, total energy intake (quartiles of kcal/wk), and occupational physical activity.

[f] Stratified according to study center, educational level, and LTPA (excluding cycling). Adjusted for sex, age, smoking status, diabetes duration, adherence to the Mediterranean diet, total energy intake (quartiles of kcal/wk), occupational physical activity, prevalent stroke, myocardial infarction, prevalent cancer, hyperlipidemia, hypertension, and central obesity.

Figure 1. Post hoc Analyses of the Associations Between Cycling or Leisure-Time Physical Activity (LTPA) (Excluding Cycling) and All-Cause or Cardiovascular Disease (CVD) Mortality



Solid lines are hazard ratios, and shading is the upper and lower bounds of the 95% CIs. Restricted cubic splines were applied (knot placements in the analyses were 0.5, 2.0, and 7.5 h/wk, and 21.1, 74.3, and 150.8 metabolic equivalent of tasks in hours per week [MET-h/wk] for cycling and LTPA, respectively). The MET-h/wk for cycling can be calculated based on the Compendium of Physical Activities using the code 01015 "Bicycling, general" with an estimated intensity of 7.5 MET-h.[34] To convert hours of cycling to MET-h, multiply by 7.5. The corresponding MET-h values for 2, 4, 6, 8, and 10 hours of weekly cycling are 15, 30, 45, 60, and 75, respectively.

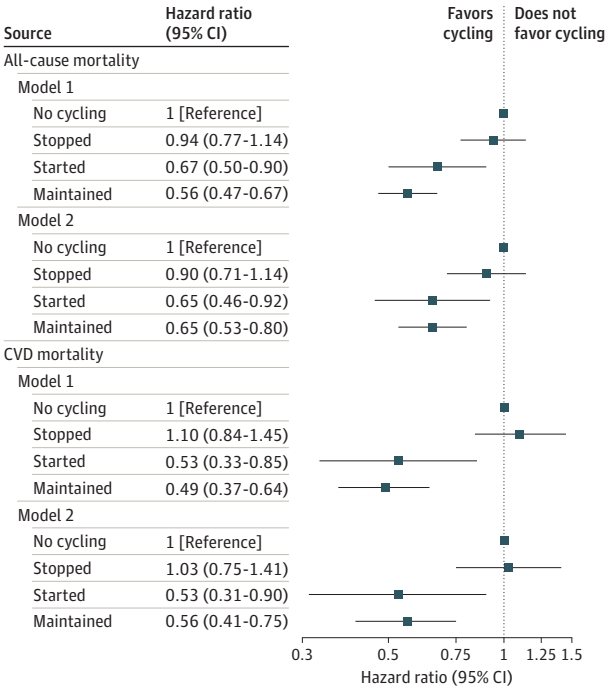
compared with cycling, may account for differences.[15] The lower risk of all-cause and CVD mortality observed in consistent cyclists or persons initiating cycling may be mediated by improvements in aerobic fitness, which is associated with all-cause and CVD mortality.[48,51]

The shapes of the dose-response curves were ambiguous. The uptick in the point estimate at high volumes of cycling can be associated with an increased risk of fatal injuries with increased cycling (eg, in urban settings or in those with increased risk of CVD or respiratory diseases owing to exposure to air pollutants during cycling in settings with dense motorized traffic).[52-54] In addition, the beneficial effects of physical activity on cardiovascular risk factors with increasing air pollutants may be attenuated.[55-58] However, previous cohort studies[36,59,60] have reported that levels of traffic-related air pollution did not modify the inverse association of outdoor physical activity with mortality or incidence of heart disease. Although air pollution during exercise may decrease lung function acutely,[55,57,58,61] it seems that the benefits of physical activity on the risk of asthma and chronic obstructive pulmonary disease are maintained when performed in moderately polluted settings such as urban environments.[62] Because cycling is associated with an increased risk of fatal injuries compared with passive transportation,[52] this may also explain the small uptick in the point estimate for all-cause mortality risk with increased cycling, but it cannot explain the corresponding shape of the curve for CVD mortality. Of note, commuter cycling may increase the risk of injuries and hospital admissions compared with nonactive commuting in the general population.[52] However, the health benefits of cycling may outweigh the increased risk of injuries owing to a decreased risk of morbidities in cyclists.[63] While data on traumatic deaths due to cycling would have enabled a benefit-harm analysis in this study, those data were unfortunately not collected. Another explanation for the uptick may be associated with potential adverse effects of very high volumes of physical activity. While a recent study does not support this in the healthy population,[64] it may constitute a concern in persons with diabetes. Participants who cycle many hours per week (eg, ≥5 h/wk) may do so at a higher intensity and thus accumulate a greater volume of physical activity compared with participants who cycle less. However, looking at the total volume of cycling (up to 75 MET-h/wk) in the context of the total volume of LTPA, it seems unlikely that this should explain the uptick because this is not observed for LTPA even at substantially higher volumes than observed with cycling. Finally, because the post hoc analyses using the average of the baseline and second examination as exposure to limit misclassification of cycling owing to change in cycling habits during follow-up to some extent attenuated the minor uptick observed when using the baseline exposure only, this suggests that the uptick might partly be a consequence of measurement error on the exposure variable. This is in line with previous observations.[65-67]

Limitations

Limitations of the study include the observational design that limits causal inferences. We were unable to distinguish between type 1 and type 2 diabetes, but generally type 2 diabetes accounts for 90% of all diabetes in adults.[68] To maximize the analytic sample, we chose to include both persons with self-reported diabetes and persons with diabetes confirmed through other sources, which increases the risk of misclassification. However, only few numerical differences were observed in the characteristics between persons with confirmed and self-reported diabetes (eTable 10 in Supplement 1), and the analysis restricted to those with confirmed diabetes only supported the overall findings. Although we adjusted the analyses

Figure 2. Association Between All-Cause or Cardiovascular Disease (CVD) Mortality and Changes in Cycling From Baseline to the Second Examination



Among noncyclists, those who stopped cycling, those who started cycling, and those who maintained cycling, person-years of follow-up were 35 674, 5923, 3571, and 12 635, respectively; cases of all-cause mortality were 598, 138, 49, and 190, respectively; and cases of CVD mortality were 247, 78, 19, and 85, respectively. Median (interquartile range) minutes of weekly cycling at baseline were 0 (0-0), 90 (60-180), 0 (0-0), and 150 (90-300) minutes for noncyclists, those who stopped cycling, those who started cycling, or those who maintained cycling, respectively. Median (interquartile range) minutes of weekly cycling at the second survey were 0 (0-0), 0 (0-0), 90 (60-210), and 150 (90-300) minutes for noncyclists, those who stopped cycling, those who started cycling, or those who maintained cycling, respectively. All-cause mortality rates per 1000 person-years were 16.8 (95% CI, 15.5-18.2), 23.3 (95% CI, 19.7-27.5), 13.7 (95% CI, 10.4-18.2), and 15.0 (95% CI, 13.0-17.3) for noncyclists, those who stopped cycling, those who started cycling, or those who maintained cycling, respectively; the corresponding incidence rates per 1000 person-years for CVD mortality were 7.0 (95% CI, 6.1-7.8), 13.2 (95% CI, 10.6-16.4), 5.3 (95% CI, 3.4-8.3), and 6.7 (95% CI, 5.4-8.3), respectively. Model 1 was stratified by study center and adjusted for sex and age (second examination). Model 2 was stratified according to study center, baseline adherence to the Mediterranean diet, baseline occupational physical activity, and total energy intake, and adjusted for sex, age (second examination), baseline educational level, smoking status at both surveys, diabetes duration at the second survey, leisure-time physical activity (excluding cycling) at both examinations, and occupational physical activity at the second examination.

for a range of potential confounders, these were mostly self-reported and thus prone to misclassification. Although slightly attenuated, the associations observed for all-cause and CVD mortality were confirmed in sensitivity analyses, when those who had ever smoked and people reporting engaging in any sports were excluded. This suggests that residual confounding by smoking and sports-related physical activity may be minor, although the 95% CIs for the latter were wide for CVD mortality. A concern may be confounding by concomitant pharmacological intervention. However, as pharmacological intervention intensifies with increasing diabetes duration,[69] and as we consistently adjusted for diabetes duration, we may, to some extent, have addressed this issue. Because the prevalence of microvascular and macrovascular complications are highly prevalent among persons with diabetes,[70] persons with a history of CVD at baseline were included in the primary analyses to increase the generalizability of the findings. While this may increase the risk of reverse causality, the 2-year benchmark sensitivity analysis did not suggest reverse causation. E-value calculations showed that to explain away the estimated associations of baseline and change in cycling with mortality with adjustment for the measured covariates, an unmeasured confounder would need to have an HR of at least 1.66 and 1.94 with both cycling and mortality, respectively. We decided a priori only to include participants with complete data for all statistical models, which could have introduced selection bias and limited generalizability. While rerunning the analyses with missing data statistically imputed for cycling and confounders confirmed the present findings, this may not fully overcome the biases. Finally, the results may not be generalizable to people using electric cycles.

Conclusions

Results of this cohort study showed that engaging in cycling was associated with a lower risk of all-cause and CVD mortality among people with diabetes after considering other physical activities as well as other risk factors. Studies with repeated measurement of cycling and documentation of cycling-related accidents are needed to elaborate on the dose-response relationship between cycling and mortality.

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