Cycling, all-cause and cardiovascular mortality among persons with diabetes: European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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KEY POINTS

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

Findings: In this prospective cohort study of 7,513 persons with diabetes, cycling was associated with a ≥24% lower all-cause mortality relative to non-cyclists, independent of other physical activity and putative confounders. Taking up cycling over a 5-yr period was associated with a ≥35% lower risk of all-cause mortality relative to consistent non-cyclists.

Meaning: Our findings suggest that cycling could be encouraged as an activity for persons with diabetes to lower the risk of mortality.

ABSTRACT

Importance: Premature death from all-causes and cardiovascular causes is higher among persons with diabetes.

Objective: To investigate the association between time spent cycling and all-cause and cardiovascular mortality among persons with diabetes, and to evaluate the association between change in time spent cycling and risk of all-cause and cardiovascular mortality.

Design: Prospective cohort study

Setting: Questionnaires were administered in eight western European countries in 1992-2000 (baseline examination) and at a 2nd examination five years after baseline.

Participants: Adults with diabetes at the baseline examination (N=7,459) from the European Prospective Investigation into Cancer and Nutrition study. A total of 5,423 participants with diabetes completed both examinations.

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 the baseline to 2nd examination.

Main outcomes and measures: The primary and secondary outcomes were all-cause and cardiovascular mortality, adjusted for other physical activity modalities, diabetes duration, socio-demographic and lifestyle factors.

Results: During 110,944 person-years of follow-up, 1,673 deaths from all-causes were registered. Compared to the reference group of people who reported no cycling at baseline, the multivariable-adjusted hazard ratios and 95% confidence intervals (95% CIs) for all-cause mortality were; 0.78 (0.61,0.99), 0.76 (0.65,0.88), 0.68 (0.57,0.82), and 0.76 (0.63,0.91) for cycling 1-59 min/week, 60-149 min/week, 150-299 min/week and 300+ min/week, 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 to people who reported no cycling at both examinations, the multivariable-adjusted hazard ratios (95% CIs) for all-cause mortality were 0.90 (0.71,1.14) in those who cycled and then stopped, 0.65 (0.46,0.92) in initial non-cyclists who started cycling, and 0.65 (0.53,0.80) for people who reported cycling at both examinations. Similar results were observed for cardiovascular mortality.

Conclusion and relevance: Cycling was associated with lower all-cause and cardiovascular 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 significantly lower risk of both all-cause and cardiovascular mortality compared to consistent non-cyclists.

BACKGROUND

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 to 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]. 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[8]. 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[9-11]. As lack of time is often quoted as a barrier, incorporating activities into everyday life, may be an effective strategy. Cycling is a potential candidate activity to replace motorized transport for short-to-medium distance trips, e.g. during commuting to work without a substantial impact on time use. As moderate-to-high intensities are reached during cycling at self-selected paces in adults [12-15], cycling could decrease the risk of premature mortality. It may also be a feasible strategy as cycling is one of the preferred activities in people with type 2 diabetes[16,17]. It is well-established that there is a strong association between cycling and improvements in cardiovascular risk factors, reduced risk of all-cause, and cause-specific mortality, such as CVD, in the general population[18-20]. There are, however, to our knowledge, no studies that have examined the role of cycling in preventing premature mortality in people with diabetes.

The primary aim of the study was to investigate the relationship between cycling and all-cause and CVD mortality among individuals with diabetes from European countries. A secondary aim was to study the relationship between change in cycling over a 5-year period and all-cause and CVD mortality.

METHODS

Study design and setting

The study is a prospective cohort study of people with diabetes at baseline in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[21]. In EPIC, 23 centers in 10 western European countries collected information on nutrition, lifestyle, anthropometry and medical history from more than 521,234 males and females participating[21]. Medical history, socio-demographic and lifestyle information was assessed by questionnaires at baseline between the year 1992-2000 (baseline examination) and at the second examination, on average 4.9 years (SD 2.1) after the baseline collection. Data were only available from 22 centers as data from Greece was not released for this study. The ethical review boards from the International Agency for Research on Cancer (IARC) and all local participating centers approved this study. All participants signed an informed consent.

Study population

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

Data collection

Study procedures have been described in detail elsewhere[21]. Briefly, height, weight, and waist circumference were measured using similar protocols across study centers[21]. Body mass index was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Central obesity was defined according the International Diabetes Federation criteria[22]. Diabetes duration was calculated as the time from self-reported age/calendar year of medical diagnosis to baseline.

Dietary intake, including alcohol consumption, was assessed by a questionnaire (quantitative, semi-quantitative, or a combination), and 7- or 14-day-record, and individual energy and nutrient intake was based on the standardized EPIC Nutrient Database (ENDB)[21,23]. As the Mediterranean diet is associated with improved metabolic control and decreased risk of diabetes[24-26], this was included as a covariate expressed as the relative Mediterranean diet score (rMED)[24,26,27]. Dietary data was 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 cycling, walking, gardening, do-it-yourself activities, household work, sports, number of stairs climbed, and occupational physical activity[21,28]. Weekly time spent cycling to/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, 1-59, 60-149, 150-299 and 300+ minutes/week. Change in total cycling from baseline to the second examination was categorized based on total time spent cycling at the two examinations 1) non-cycling - participants who reported zero minutes of cycling at both examinations, 2) people who stopped cycling - those who reported cycling (any amount) at the baseline but not the second examination, 3) people who started cycling - participants who did not report cycling at baseline but did report cycling (any amount) at the second examination or 4) those who were consistent cyclists at both examinations.

LTPA energy expenditure (without cycling included – from here on denoted LTPA) (metabolic equivalent of task -MET-h/week) 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. The MET-h/week expresses the intensity of physical activity (PA) as multiples of the resting metabolic rate[14]. As information on stair-climbing was only available from four 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/heavy manual work, or non-worker[28].

Outcome ascertainment

The primary and secondary outcomes were all-cause and CVD mortality, respectively. CVD deaths were coded according to the *International Classification of Diseases, Injuries, and Causes of Death, Tenth Revision*, using the codes I00-I99. Vital status and cause of death were obtained through record linkage with national, regional or local registries, regional health departments, physicians or hospitals, active follow-up, or health insurance[29].

Statistical analysis

A statistical analysis plan was developed (see supplementary material), published at *http://aktivsundhed.dk/da/cfas-forskning/publikationsliste,* and pre-registered at www.clinicaltrials.gov (identifier NCT04171557) prior to commencing the analyses. The risks of all-cause and CVD mortality were computed as hazard ratios (HRs) with 95% confidence intervals (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 due to emigration or premature withdrawal were right censored at the age of emigration or withdrawal. As the associations between baseline cycling , all-cause or CVD mortality were non-linear, we computed restricted cubic splines of the respective relationships with knot placements at the 10^{th}, 50^{th} and 90^{th} percentiles as recommended by Harrell[30]. Due to large amounts of zero values in the cycling variable, the percentiles were computed excluding zero.

A crude model (Model 1) was fitted with categories of cycling as exposure (0 (reference), 1-59, 60-149, 150-299 and 300+ minutes/week) and 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 school, secondary school, or university degree), smoking status (never-smoker, former smoker, or current smoker), diabetes duration (years), adherence to the Mediterranean diet score (categories of the rMED score, low: 0–6 points, medium: 7–10 points, or high: 11–18 points) [24,26], total energy intake (quartiles of kcal/day)[23], physical activity excluding cycling (quartiles of LTPA energy expenditure), and occupational PA (sedentary occupation, standing occupation, manual/heavy manual work, non-worker or unknown status) (*Model 2, main model*). Finally, prevalent stroke, (yes/no), previous myocardial infarction (MI, (yes/no)), prevalent cancer (yes/no), hypertension (yes/no), hyperlipidemia (yes/no), and central obesity (yes/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 (Model 2). Because several covariates did not meet the proportional hazard assumption in the multivariable Models 2 and 3, we computed an extended Cox regression analysis where we stratified by study center and energy intake in the analyses with the 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 pre-planned sensitivity analyses for the primary model *(Model 2)* specified in *the statistical analysis plan* to investigate the impact of residual confounding and reverse causality (excluding all deaths and CVD deaths within the first 2 years following the baseline examination).

In the pre-planned secondary analysis, associations between all-cause and CVD mortality, and change (from baseline to second examination) in cycling 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, leisure-time physical activity excluding cycling at both examinations, and occupational physical activity at the second survey). The multivariable analyses were stratified by study center, baseline occupational physical activity, adherence to the relative Mediterranean diet and total energy intake at baseline.

Ten-year adjusted (standardized) cumulative mortality according to cycling at baseline or change in cycling status, consistent with the primary models, were estimated using flexible parametric survival models[31], with additional post estimation of adjusted differences (95% CI) in 10-year cumulative mortality comparing 0 min/week of cycling at baseline and/or at the second examination to higher levels of cycling or stopping/starting/maintaining cycling.

All analyses were conducted using STATA IC V.16.1 (STATA Corp, College Station, Texas, USA) using α=0.05 (2-sided).

RESULTS

Of the 492,763 participants enrolled into the EPIC cohort, 10,995 had diabetes at the baseline examination. The analytic sample consisted of 7,459 participants (63% with confirmed diabetes) with a mean age (standard deviation ((SD)) of 55.9 (7.7) years, a mean diabetes duration (SD) of 7.7 (8.1) years and of who 52.6 % were female. Baseline characteristics are shown in Table 1 and the flow of participants with main reasons of exclusion is found in eFigure 1.

The participants were followed for a mean (SD) of 14.9 (4.4) years (110,944 person-years) with 1,673 deaths from all-causes and 811 deaths attributable to CVD. A subset of participants also completed the 2nd examination and were included in the analysis of change in cycling (n=5,423). This analysis had a mean (SD) of 10.7 (4.3) years follow-up accumulating a total of 57,802 person-years with 975 deaths from all-causes and 429 from CVD.

Baseline cycling, all-cause and CVD mortality

Time spent cycling at baseline was inversely associated with the risk of all-cause and CVD mortality in the crude model (Table 2, Model 1). A lower HR for all-cause mortality was observed for all people reporting any cycling (>0 min/week), when compared to non-cyclists. 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 affect the relationship between cycling and all-cause mortality (Table 2, Model 2). Adjusted 10-year cumulative mortality per category is found in eTable 1 and eFigure 2. The cumulative mortality risk difference (RD) relative to 0 min/week of cycling for ascending cycling categories were of -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 1). No significant multiplicative interactions of sex or diabetes duration and cycling were observed for all-cause nor CVD mortality. Further adjustment for existing conditions and CVD risk factors only slightly attenuated the associations (Table 2, Model 3). 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 3).

The dose-response relationship with baseline cycling as a continuous variable for both all-cause and CVD mortality was modelled (Figure 1). For comparison, the relationship for LTPA (excluding cycling) is provided. This revealed a reversed J-shaped association between both outcomes and cycling and a linear association for LTPA (excluding cycling) (HRs (95% CIs) per 10 MET-h increase per week: 0.97 (0.95, 0.98) and 0.96 (0.94, 0.98) for all-cause and CVD mortality, respectively) (Figure 1).

Change in cycling and all-cause and CVD mortality

The associations between change in cycling between baseline and second examination (no cycling, ceased, initiated, and continued cycling) , and all-cause and CVD mortality are shown in Figure 2. For both outcomes, HRs were ≥35% lower among participants who started or maintained cycling (Figure 2) relative to non-cyclist (RD relative to non-cyclist were -3.7% for all-cause and -2.7% for CVD mortality, eTable 2, eFigure 3). After excluding deaths within the first two years from the follow-up examination, the associations were unchanged; HRs (95% CIs) for all-cause mortality were 0.93 (0.72, 1.19), 0.66 (0.45, 0.95), and 0.64 (0.51, 0.80) for people who stopped, started or maintained cycling, compared to non-cyclists. Corresponding HRs (95% CIs) for CVD mortality were 1.08 (0.77, 1.51), 0.56 (0.31, 0.99), and 0.54 (0.39, 0.75).

DISCUSSION

In this European prospective cohort study, 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, sociodemographic factors and a range of other lifestyle and clinical risk factors including diet quality and central obesity. Change over time in cycling was also related to mortality risk, with a significantly lower mortality risk for people with diabetes who took up cycling between two examinations five years apart.

The importance of cycling in relation to mortality risk has been studied extensively in disease free populations[12,19,20,32], and the associated relative risks for all-cause and CVD mortality associated with cycling in this study in people with diabetes, were similar in magnitude and direction [33-38]. 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[7,8,39-45]. This 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 person with diabetes[46]. However, the association was weaker as compared to our observations. As physical activity intensity is important in mediating the health benefits from walking among people with type 2 diabetes [8,47], a lower intensity of physical activity, such as walking, when compared to cycling, may account for differences[14]. 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[45,48].

While it is biologically plausible that regular engagement in cycling would reduce all-cause and CVD mortality in persons with diabetes, the dose-response curves are ambiguous. It is important to note that only a few diabetic participants reported very high volumes of cycling, and the confidence intervals are very wide, and we cannot not reject the existence of a monotonic dose-response relationship. Also, the analysis of change in cycling habits over a five-year period showed lower mortality risk among diabetic people who started cycling compared with those, which provide support of a possible causal relationship. However, we cannot exclude other causes of the indication of a reversed j-shaped relationship or lack of a monotonic relationship between cycling and mortality in diabetic people. The "upstick" in risk at high volumes can also relate to an increased risk of fatal injuries with increased cycling, e.g. in urban settings or increased risk of CVD or respiratory diseases due exposure to air pollutants during cycling in settings with dense motorized traffic[49-51]. In addition, the beneficial effects of physical activity on cardiovascular risk factors with increasing air pollutants may be attenuated[52-55]. However, previous cohort studies 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.[33,56,57]. Although air pollution during exercise may decrease lung function acutely[52,54,55,58], it seems that the benefits of physical activity on the risk of asthma and COPD is maintained when performed in moderately polluted settings such as urban environments[59]. As cycling is associated with and increased risk of fatal injuries compared with[49], this may also explain the small "upstick" in all-cause mortality risk with increased cycling, but 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 to non-active commuting in the general populations[49]. However, the health benefits of cycling may outweigh the increased risk of injuries due to a decreased risk of morbidities in cyclists[60]. Finally, bias due to uncontrolled confounding and reverse causation may also explain the lack of a monotonic relationship.

Strengths and limitations

The study includes a range of countries including those with established cycling infrastructures and cultures, such as Denmark and The Netherlands and others were cycling is less common. The inclusion of data from a follow-up examination approximately 5 years after baseline examination which allowed us to investigate within-person change in cycling exposure and its relationship with subsequent mortality risk.

Limitations of the study include the inability to distinguish between type 1 and type 2 diabetes. Generally, type 2 diabetes accounts for 90% of all diabetes cases in adults[61]. Therefore, we assume our findings primarily apply to persons with type 2 diabetes. To maximize the analytic sample, we chose to include both self-reported cases and diabetes cases confirmed through other sources, which increases the risk of misclassification. However, only few numerical differences were observed in the characteristics between confirmed and self-reported diabetes (eTable 2). Also, findings from a sensitivity analysis, where we restricted to those with confirmed diabetes cases only, supported our overall findings. Although we adjusted the analyses 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 ever-smokers 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[62], and as we consistently adjust for diabetes duration, we may, to some extent, have addressed this issue in our analyses. As the prevalence of micro- and macrovascular complications are highly prevalent among persons with diabetes [63], persons with a history of CVD at baseline were included in the primary analyses to increase the generalizability of the findings. However, such complications may limit engagement in physical activity, including cycling, thus increase the risk of reverse causation. Our sensitivity analyses excluding participants with a history of MI, stroke, and prevalent cancer as well as all those dying within 2 years of follow-up did however not materially change the interpretation. Finally, we decided *a priori,* only to include participants with complete data for all statistical models, which could have introduced selection bias and limited generalizability. However, rerunning the analyses with missing data statistically imputed for cycling and confounders, confirmed our findings. The results may not be generalizable to people using electric cycles.

In conclusion, engaging in cycling was related to a lower risk of all-cause and CVD mortality among people with diabetes after considering other physical activities, as well as other risk factors.

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Figure legends

Figure 1 Post hoc analyses of the relationships between cycling (hours/week) or leisure time physical activity (LTPA) excluding cycling (metabolic equivalent of tasks per week (MET hours/week)) and all-cause mortality (Panel A and B) or cardiovascular (CVD) mortality (Panel C and D) based on Model 2. Solid lines are hazard ratios (HR) and dotted lines are the upper and lower bounds of the

95% confidence intervals (CI). Restricted cubic splines were applied (knot placements in the analyses were 0.5, 2.0, 7.5 hours/week and 21.1, 74.3 and 150.8 met*hours per week for cycling and LTPA, respectively).

Figure 2 The association between all-cause or cardiovascular mortality and changes in cycling from the baseline to the 2nd examination. Data are presented as hazard ratios with 95% confidence intervals (error bars). Person-years of follow-up/N_{cases} all-cause mortality/ N_{cases} cardiovascular mortality for non-cyclists (35,674/598/247), those who stopped (5,923/138/78), started (3,571/49/19), or maintained cycling (12,635/190/85). Median minutes (interquartile range) of weekly cycling at baseline were 0 (0-0), 90 (60-180), 0 (0-0) and 150 (90-300) minutes for non-cyclists, those who stopped, started or maintained cycling, respectively. Median minutes (interquartile range) of weekly cycling at the 2nd survey 0 (0-0), 0 (0-0), 90 (60-210) and 150 (90-300) minutes for non-cyclists, those who stopped, started or maintained cycling respectively. All-cause mortality rates per 1000 person-years (95% confidence intervals) were 16.8 (15.5, 18.2), 23.3 (19.7, 27.5), 13.7 (10.4, 18.2) and 15.0 (13.0, 17,3) for non-cyclists, those who stopped, started or maintained cycling, respectively. The corresponding incidence rates per 1000 person-years (95% confidence intervals) for cardiovascular mortality were 7.0 (6.1, 7.8), 13.2 (10.6, 16.4), 5.3 (3.4, 8.3) and 6.7 (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, 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 activity (excluding cycling) at both examinations and occupational physical activity at the second examination.

Authors contributions: MR-L, MGR, KB, LBA, SB and LBA contributed to the design and interpretation of the data. MGR performed the statistical data analyses under supervision of AG and MR-L. MG-R, AG and MR-L had access to the final dataset for the study provided by the International Agency for Research on Cancer / World Health Organization and takes responsibility for the integrity of the dataset and the accuracy of the data analysis. MR-L wrote the first draft of the manuscript with contributions from MGR and AG. All authors contributed to a critical revision of the initial manuscript and approved the final version of the report.

Reproducible Research Statement Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures and appendices) can accessed by contacting the International Agency for Research on Cancer / World Health Organization. Analytic codes are available upon request by contacting the corresponding author. MR-L and MGR 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.

Conflict of Interest Disclosures None of the authors reports a conflict of interest

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Table 1. Baseline characteristics of sample subgroups and the total cohort

	Weekly time spent cycling at first examination					
	0 min.	0-59 min.	60-149 min.	150-299 min.	300+ min.	Total
N	4,648	422	999	736	654	7,459
Average annual cycling (min./week) ‡	0 (0-0)	30 (30-30)	90 (60-120)	180 (165-240)	420 (330-600)	0 (0-90)
Sex (% male/female)	42.4/57.6	59.5/40.5	56.2/43.8	54.5/45.5	53.5/46.5	47.4/52.6
Age (years)†	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 (years) †	7.7 (8.1)	7.3 (7.4)	7.7 (8.4)	7.7 (8.1)	7.5 (8.0)	7.7 (8.1)
Education (%)						
None	23.4	1.4	4.2	3.7	2.8	15.8
Primary school completed	35.3	42.4	35.4	40.1	43.9	37.0
Technical/professional school	17.1	23.2	27.7	28.5	29.5	21.1
Secondary school	8.4	10.2	10.7	9.0	8.9	8.9
Longer education (incl. University deg.)	15.9	22.7	21.9	18.8	15.0	17.3
Smoking (%)						
Never	50.8	38.2	40.0	41.3	38.4	46.6
Former	26.7	38.9	37.3	37.0	41.0	31.1
Current	22.4	23.0	22.6	21.7	20.6	22.3
BMI (kg/m^2)†	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 (cm)†						
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 (N (%) - yes/no)	3681 (79.2)/967 (20.8)	280 (66.4)/142 (33.6)	707 (70.8)/292 (29.2)	558 (75.8)/178 (24.2)	487 (74.5)/167 (25.5)	5,713 (76.6)/1,746 (23.4)
Leisure time physical activity without cycling, MET-h/week‡						
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	21.4	28.7	25.8	23.4	18.2	22.3
Standing occupation	20.7	19.0	17.9	18.6	16.8	19.7
Manual work	9.3	11.6	11.2	11.4	10.6	10.0
Non worker	47.4	40.0	44.2	45.0	51.4	46.7

Unknown	1.2	0.7	0.8	1.6	3.1	1.3
Energy intake (kcal/day)†	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 the relative Mediterranean diet score (%)						
Low	16.6	21.1	30.1	28.8	31.0	21.1
Medium	43.2	54.7	49.9	51.4	47.7	45.9
High	40.2	24.2	19.9	19.8	21.3	32.9
Prevalent co-morbidities						
Prevalent cancer (%)	4.4	4.0	3.8	4.6	5.4	4.4
Stroke (%)	3.4	2.6	3.6	2.3	2.4	3.2
Myocardial infarction (%)	4.8	5.5	5.6	5.2	5.4	5.1
Hyperlipidaemia (%)	41.8	46.0	36.1	37.8	38.5	40.6
Hypertension (%)	47.3	48.1	48.5	48.8	53.2	48.2

† Mean (standard deviation), ‡ Median (Interquartile range: First quartile-Third quartile),
MET-h/week; Metabolic equivalent of task – hours per week, n, number, min, minutes, BMI, body mass index,
To convert cm to inches divide by .39

Table 2. Association between total volume of cycling at the baseline examination and all-cause and cardiovascular disease mortality

	Weekly time spent cycling at first examination				
	0 min.	1-59 min.	60-149 min.	150-299 min.	300+ min.
N	4,648	422	999	736	654
Person-years	70,741	5,994	14,395	10,521	9,292
Cases – All cause mortality	1,059	79	231	150	154
Mortality rate/1000 person-years	14.9 (14.1, 15.9)	13.2 (10.6, 16.4)	16.0 (14.1, 18.3)	14.3 (12.2, 16.7)	16.6 (14.2, 19.4)
Model 1 (HR and (95% CI))[1]	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 (HR and (95% CI))[2]	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 (HR and (95% CI))[3]	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 - Cardiovascular mortality	499	41	119	66	86
Mortality rate/1000 person-years	7.1 (6.5, 9.3)	6.8 (5.0, 9.3)	8.3 (6.9, 9.9)	6.3 (4.9, 8.0)	9.3 (7.5, 11.4)
Model 1 (HR and (95% CI))[1]	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 (HR and (95% CI))[4]	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 (HR and (95% CI))[5]	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)

HR; Hazard ratio, CI; Confidence interval, N, number for persons; min., minutes
*Median and interquartile range

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

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

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

[4] Stratified according to study center, educational level, and leisure-time physical activity (excluding cycling). Adjusted for sex, age, smoking status, diabetes duration, adherence to the Mediterranean diet, total energy intake and occupational physical activity

[5] Stratified according to study center, educational level, and leisure-time physical activity (excluding cycling). Adjusted for sex, age, smoking status, diabetes duration, adherence to the Mediterranean diet, total energy intake and occupational physical activity, prevalent stroke, prevalent myocardia infarction, prevalent cancer, hyperlipidemia, hypertension and central obesity

Exposure variables were obtained at the baseline (1st) examination

Fig 1:

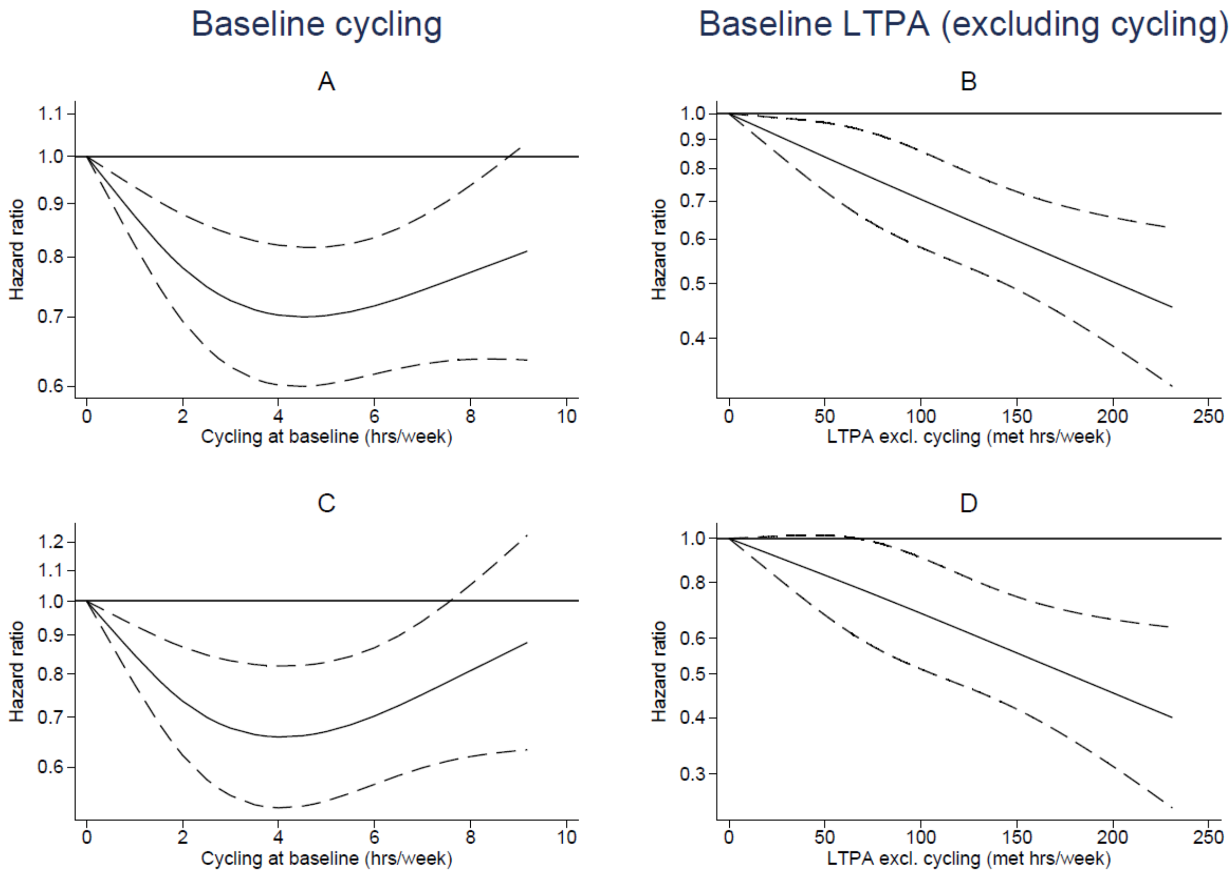
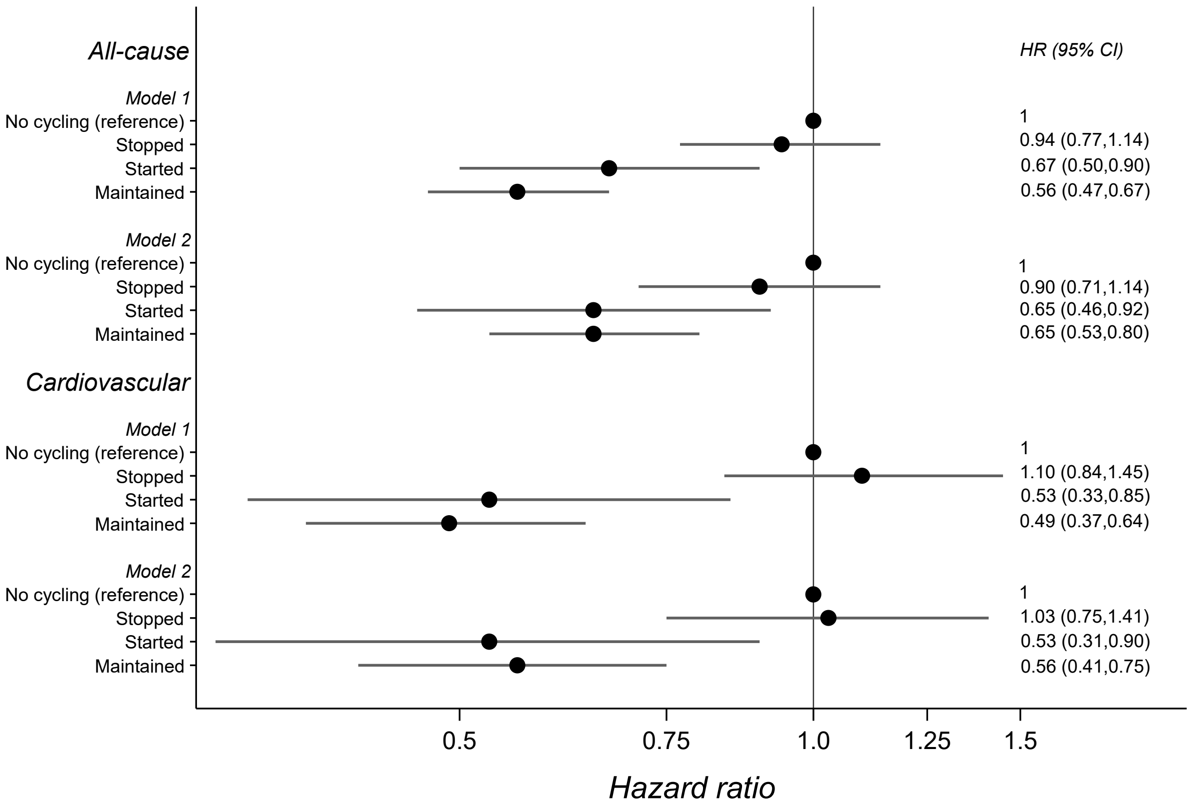

Baseline cycling
Baseline LTPA (excluding cycling)
A
B
C
D
Hazard ratio
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
2
4
6
8
10
Cycling at baseline (hrs/week)
50
100
150
200
250
LTPA excl. cycling (met hrs/week)

Fig 2:



All-cause
HR (95% CI)
Model 1
No cycling (reference)
Stopped
Started
Maintained
1
0.94 (0.77,1.14)
0.67 (0.50,0.90)
0.56 (0.47,0.67)
Model 2
No cycling (reference)
Stopped
Started
Maintained
1
0.90 (0.71,1.14)
0.65 (0.46,0.92)
0.65 (0.53,0.80)
Cardiovascular
Model 1
No cycling (reference)
Stopped
Started
Maintained
1
1.10 (0.84,1.45)
0.53 (0.33,0.85)
0.49 (0.37,0.64)
Model 2
No cycling (reference)
Stopped
Started
Maintained
1
1.03 (0.75,1.41)
0.53 (0.31,0.90)
0.56 (0.41,0.75)
0.5
0.75
1.0
1.25
1.5
Hazard ratio