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Leisure-time physical activity and all-cause mortality and cardiovascular disease in adults with type 2 diabetes: Cross-country comparison of cohort studies

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Abstract

Purpose: This study aimed to quantify the dose–response association and the minimal effective dose of leisure-time physical activity (PA) to prevent mortality and cardiovascular disease in adults with type 2 diabetes.

Methods: Cross-country comparison of 2 prospective cohort studies including 14,913 and 17,457 population-based adults with type 2 diabetes from the UK and China. Baseline leisure-time PA was self-reported and categorized by metabolic equivalent hours per week (MET-h/week) according to World Health Organization recommendations: none, below recommendation (>0–7.49 MET-h/week); at recommended level (7.5–14.9 MET-h/week); above recommendation (≥15 MET-h/week). Mortality and cardiovascular disease data were obtained from national registries.

Results: During a median follow-up of 12.4 and 9.7 years, in the UK and China cohorts, repectively, higher levels of leisure-time PA were inversely associated with all-cause (1571 and 2351 events) and cardiovascular mortality (392 and 1060 events), mostly consistent with a linear dose–response relationship. PA below, at, and above recommendations, compared with no activity, yielded all-cause mortality hazard ratios of 0.94 (95% confidence interval (95%CI): 0.79–1.12), 0.90 (95%CI: 0.74–1.10), and 0.85 (95%CI: 0.70–1.02) in British adults and 0.87 (95%CI: 0.68–1.10), 0.88 (95%CI: 0.74–1.03), and 0.77 (95%CI: 0.70–0.85) in Chinese adults. Associations with cardiovascular mortality were more pronounced in British adults (0.80 (95%CI: 0.58–1.11), 0.75 (95%CI: 0.52–1.09), and 0.69 (95%CI: 0.48–0.97)) but less pronounced in Chinese adults (1.06 (95%CI: 0.76–1.47), 1.01 (95%CI: 0.80–1.28), and 0.79 (95%CI: 0.69–0.92)). PA at recommended levels was not associated with lower rates of major adverse cardiovascular events (2345 and 4458 events).

Conclusion: Leisure-time PA at the recommended levels was not convincingly associated with lower mortality and had no association with risk of major adverse cardiovascular events in British or Chinese adults with type 2 diabetes. Leisure-time PA above current recommendations may be needed to prevent cardiovascular disease and premature mortality in adults with type 2 diabetes.

Keywords: Complications; Epidemiology; Exercise; Prevention

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1. Introduction

Globally, more than 1 in 11 adults have diabetes, of whom more than 90% have type 2 diabetes.[1] Despite an impressive reduction in excess mortality among adults with type 2 diabetes from high-income countries during the last 2 decades,[2,3] the life expectancy gap remains substantial.[4] The American Diabetes Association states that caregivers, patients and societies should focus on optimizing healthy lifestyle behaviors, such as physical activity (PA), to improve diabetes care and reduce risk of complications and death.[5] However, individuals with type 2 diabetes are less physically active than individuals free from chronic diseases.[6]

For adults with type 2 diabetes, contemporary PA guidelines are quantitatively identical to those given to the general population (i.e., 150−300 min of moderate-to-vigorous PA per week[5,7]). Based on limited data, only 40%−60% of adults with type 2 diabetes meet this recommendation in high-income countries.[8,9] The guidelines, updated by the World Health Organization (WHO) in 2020, emphasize that PA below the recommended level will result in health benefits for all adults because the dose−response association is highly curvilinear.[10] Therefore, the largest health gains can be obtained by moving inactive adults from doing no activity to doing some PA. This message has substantial clinical implications as doing a little PA may be a feasible target for many patients. Yet, for adults with type 2 diabetes, key issues with respect to the dose−response relationship between PA and mortality and cardiovascular disease (CVD), including the minimal effective dose needed to prevent outcomes, are not underpinned by high-quality evidence.[7]

Another cause for concern is the lack of evidence from low- and middle-income countries,[11−14] which are home to 80% of the global population of adults with type 2 diabetes.[15] Differences in healthcare, economy, culture, genetic predispositions to type 2 diabetes, and conditions and distributions of PA behaviors mean evidence from high-income countries may not be transferable to other contexts. Concomitantly, consistent exposure−outcome associations across different contexts provide greater confidence in the totality of the evidence.[16]

Accordingly, the aim of this study was to quantify and compare the dose−response associations of leisure-time PA with all-cause mortality and CVD in British and Chinese adults with type 2 diabetes.

2. Methods

2.1. Study design and setting

The current study is based on the UK Biobank and the China Kadoorie Biobank population-based prospective cohorts. For the UK Biobank study, 502,682 participants (approximately 5.5% of those invited) aged 37−82 years were recruited via 22 assessment centers across England, Wales, and Scotland between 2006 and 2010.[17] For the China Kadoorie Biobank study, 512,891 participants (approximately 30% of those invited) aged 30−79 years were recruited between 2004 and 2008 from 10 regions of the mainland of China.[18] The UK Biobank was approved by the Northwest Multi-Centre Research Ethical Committee (Reference number: 11/NW/03820). The China Kadoorie Biobank was approved by the Ethics Committees at Oxford University and the China National Center for Disease Control and from institutional research boards at the local Centers for Disease Control in the 10 included regions. Participants provided written informed consent.

2.2. Study population

We identified adults with prevalent type 2 diabetes in the UK Biobank by the Eastwood algorithm[19] and/or from a measured hemoglobin A1c (HbA1c) ≥ 48 mmol/mol. The Eastwood algorithm is based on combining several sources of information, including diabetes diagnosis, age of diabetes diagnosis, ethnicity and use of medication based on a questionnaire and an interview with a trained nurse. We included participants from the UK Biobank baseline examination and from the repeat assessment conducted from 2012 to 2013 (i.e., individuals developing type 2 diabetes since their participation in the baseline assessment). Data collected at the repeat assessment was used as baseline for these participants. In China Kadoorie Biobank, prevalent type 2 diabetes was defined from self-reported current diabetes with a diagnosis age above 30 years, a random plasma blood glucose ≥ 11.1 mmol/L, or a fasting plasma blood glucose ≥ 7.0 mmol/L.

2.3. Data collection

In both studies, sociodemographic, behavioral, and health-related information were collected at local assessment centers, where participants also provided biological samples.[20,21] Information about covariates used for this study is provided in Supplementary Table 1 of Supplementary File 1. Body mass index (BMI) was calculated from measured height and weight. Years since diagnosis was used as a proxy of diabetes duration and calculated as age at examination minus self-reported age at diabetes diagnosis. Individuals with undiagnosed type 2 diabetes identified from baseline biochemistry measurement were assigned a diabetes duration of 0. Prevalent medical conditions at baseline were identified from self-report and hospital records in the UK Biobank and from self-report in the China Kadoorie Biobank.

2.4. Assessment of PA

PA was self-reported on a touch-screen questionnaire in UK Biobank and by an interviewer-assisted questionnaire in China Kadoorie Biobank. The questionnaires covered information on the frequency, duration, and type of leisure-time PA. Responses were combined to calculate the total volume of leisure-time PA in metabolic equivalents of task (MET)-h/week (additional details in Supplementary Table 1 of Supplementary File 1). MET-h/week were classified into 4 mutually exclusive categories based on the WHO and American Diabetes Association PA recommendations of 150−300 min of aerobic moderate-to-vigorous PA per week (assuming 3 METs as

moderate activity[14]): no leisure-time PA, below recommendation (>0−7.49 MET-h/week), at recommended level (7.5−14.9 MET-h/week), above recommendation (≥15 MET-h/week).[5,10] Quality control was performed by excluding implausible values defined as the sum of self-reported behaviors exceeding 24 h/day. PA for transportation was categorized as passive, walking, or cycling. Occupational PA was classified as sedentary, standing, or manual/heavy manual work.

2.5. Outcome ascertainment

All-cause mortality and CVD, defined as cardiovascular mortality and major adverse cardiovascular events, were obtained through linkage to national registries. All-cause mortality was the pre-specified primary outcome, cardiovascular mortality and incidence are secondary outcomes. Participants were followed until death, emigration, loss to follow-up, withdrawal from the study, or end of observation time (Supplementary Table 2 of Supplementary File 1), whichever occurred first. Cardiovascular mortality and major adverse cardiovascular events were coded according to the *International Classification of Diseases, Injuries, and Causes of Death*, 10th Revision. Cardiovascular mortality was any primary cause of death coded as I00 to I99. Major adverse cardiovascular events included the first incident episode of ischemic heart disease (I20−I25) or stroke (I60, I61, I63, and I64) identified from hospital records, in addition to cardiovascular mortality.

2.6. Statistical analysis

A statistical analysis plan was developed and registered at ClinicalTrials.gov (NCT05380232, Supplementary File 2) *prior to* commencing the analysis. To limit the potential influence of major somatic or psychological conditions leading to reduced PA (i.e., reverse causation), we excluded participants if they had any of the conditions listed in Supplementary Table 3 of Supplementary File 1 (UK Biobank: $n = 6310$; China Kadoorie Biobank: $n = 1679$). This list of conditions is not intended to be complete but to remove individuals with very severe medical conditions based on available data (e.g., chronic degenerative neurological problems, renal failure, or chronic obstructive pulmonary disease) as well as those individuals with conditions most likely to interfere with engagement in PA (e.g., inability to walk or chronic widespread pain). In our primary analyses, we also excluded individuals with a history of pre-existing CVD or cancer at baseline (definitions provided in Supplementary Table 3 of Supplementary File 1, UK Biobank: $n = 4163$; China Kadoorie Biobank: $n = 3900$). Individuals with pre-existing CVD were included in a secondary analysis. Participant flowcharts are presented in Supplementary Fig. 1 of Supplementary File 1.

Statistical adjustment was informed by a cohort-specific directed acyclic graph (Supplementary File 2). Associations are presented as hazard ratios (HRs) with 95% confidence intervals (95%CIs) from Cox proportional hazards regression models. Age was modeled as the timescale, and follow-up started 3 years after the baseline assessment (delayed entry). Cohorts were analyzed separately based on 4 regression models with incremental levels of adjustment. Model 1: age and sex adjusted. Model 2: Model 1 + sociodemographic variables, lifestyle factors (smoking, dietary quality indicators, alcohol intake, PA for transportation and occupation), family history of diabetes/cancer/CVD, inclusion method (self-reported type 2 diabetes/use of diabetes medication or biochemistry), poor mental health, and diabetes duration. Model 3 (main model): Model 2 with further adjustment for BMI (conceptualizing BMI as a source of confounding[22,23]). In an additional Model 4, we further adjusted our main model for pharmacological treatment of blood glucose, lipids, and blood pressure as potential mediating factors.

The continuous dose−response pattern was modeled based on the main model using a restricted cubic spline. Because many participants had 0 MET-h/week, 3 knots were placed at the 10th median and 90th percentiles of the exposure distribution among participants with non-zero leisure-time PA. Departure from linearity was assessed by a Wald test of the null-hypothesis that the coefficient of the second spline is equal to 0.[24] MET-h/week was winsorized at the 95th percentile in these analyses because the highest values are at the greatest risk of reporting error. Absolute risk differences were estimated as the standardized 10-year cumulative mortality using a flexible parametric survival model (not specified in the pre-defined analysis plan).[25]

Effect modification by sex, whether the patient was identified with type 2 diabetes from self-report or biochemistry, age (<60 *vs.* ≥60 years old), diabetes duration (<5 *vs.* ≥5 years), and by a history of pre-existing CVD was examined by stratification and evaluated statistically using the likelihood-ratio test. The pre-defined statistical analysis plan specified an analysis repeating model 3 including both individuals with and without pre-existing CVD. Instead, we repeated Model 3 but restricted it to individuals with pre-existing CVD only in order to provide estimates directly applicable to this group of high-risk patients. Finally, we performed sensitivity analyses by re-analyzing our data (using Model 3) restricted to never smokers and adjusting for more detailed diet information from 24-h recalls conducted between 2009 and 2012 (UK Biobank, subsample only), and restricted to individuals classified as "possible type 2 diabetes" who had HbA1c < 48 mmol/mol (UK Biobank).

The proportional hazards assumption was verified by log−log plots and by Schoenfeld residuals plotted against follow-up time. Cardiovascular mortality and major adverse cardiovascular events were modeled using Fine-Gray models[26] with death from other causes as a competing event. Statistical analyses were performed using Stata Version 16.0 (StataCorp., College Station, TX, USA). Statistical significance was $\alpha = 0.05$ (two-sided).

3. Results

We identified 29,236 (5.8%) and 30,155 (5.9%) adults with type 2 diabetes in the UK Biobank and China Kadoorie biobank, respectively. From these, a total of 14,913 and 17,457 participants with type 2 diabetes and no history of

CVD, cancer, or other major comorbidities at study baseline were included. During a median follow-up of 12.4 and 9.7 years after baseline, 1571 and 2351 deaths (392 and 1060 deaths from CVD) and 2345 and 4458 major adverse cardiovascular events were included from the UK Biobank and China Kadoorie Biobank, respectively. The age of participants was similar, at 59.5 ± 7.2 years and 57.8 ± 9.7 years (mean ± SD), but the distributions of sex, BMI, leisure-time PA, diabetes duration, use of preventive medications, and the proportion of undiagnosed diabetes were different. More than half of Chinese participants did no PA in their leisure-time while this was the case for only 9% of British participants. The mean differences in BMI between participants with no PA and those exceeding recommendations was 3.4 kg/m^2 in the UK Biobank but only 0.2 kg/m^2 in the China Kadoorie Biobank. More physically active participants had completed more formal schooling in both cohorts. Descriptive characteristics across categories of MET-h/week are presented in Table 1 and in greater detail in Supplementary Tables 4 and 5 of Supplementary File 1. Distributions of leisure-time PA among cases and in all participants are shown in Supplementary Fig. 2 of Supplementary File 1.

3.1. Leisure-time PA and all-cause mortality

Higher levels of leisure-time PA were associated with lower all-cause mortality in both cohorts (Table 2). Statistical adjustment for BMI attenuated associations in the UK Biobank but did not impact effect sizes in the China Kadoorie Biobank. In the UK Biobank, the slope of the dose−response association was shallow below 15 MET-h/week, accelerated thereafter, and reached statistical significance at 35 MET-h/week, which is equivalent to 90 min of walking or 38 min of strenuous sports per day (Fig. 1, p for non-linearity = 0.51). No upper level of additional risk reduction was observed within the exposure distribution. In categorical analyses, PA below recommendations, compared with no activity, was associated with a slight and uncertain reduction in all-cause mortality, with an HR of 0.94 (95%CI: 0.79−1.12). The dose−response association in China Kadoorie Biobank suggested a curvilinear relationship ($p = 0.03$), with lower mortality for any non-zero level of leisure-time PA and no additional risk reduction above 35 MET-h/week. The HR for PA below recommendations was 0.87 (95%CI: 0.68−1.10). The absolute differences in 10-year cumulative mortality, compared with no activity, were −0.2%, −0.4%, and −0.6% in the UK Biobank and −1.4%, −1.3%, and −1.6% in the China Kadoorie Biobank for PA below, at, and exceeding recommendations (Supplementary Table 6 of Supplementary File 1).

3.2. Leisure-time PA and cardiovascular mortality and major adverse cardiovascular events

Continuous dose−response curves were supportive of a linear relationship with cardiovascular mortality in both cohorts ($p \geq 0.67$) with a steeper slope in the UK Biobank. There was no upper threshold of additional risk reduction in either cohort. The HRs for PA below and above recommendations were 0.80 (95%CI: 0.58−1.11) and 0.69 (95%CI: 0.48−0.97) in the UK Biobank and 1.06 (95%CI: 0.76−1.47) and 0.79 (95%CI: 0.69−0.92) in the China Kadoorie Biobank. PA at recommended levels was not associated with cardiovascular mortality in the China Kadoorie Biobank. There was no association between leisure-time PA below or at recommended levels and risk of major adverse cardiovascular events in either cohort (Table 2). Doing more than 35 MET-h/week yielded HRs from 0.87 (95%CI: 0.77−0.99) to 0.82 (95%CI: 0.71−0.96) in the UK Biobank.

3.3. Stratified and sensitivity analyses

Additional adjustment for pharmacological treatment slightly attenuated associations in the UK Biobank (Model 4). Stratified associations with all-cause mortality are shown in Fig. 2. Age modified the association in the China Kadoorie Biobank, with an HR for PA exceeding recommendations of 0.95 (95%CI: 0.78−1.14) among adults <60 years old and 0.72 (95%CI: 0.64−0.81) among those ≥60 years old (p for interaction < 0.001). There was no evidence of effect modification by pre-existence of cardiovascular morbidity (effect modification p values 0.97 and 0.79).

The pattern of results did not change with exclusion of ever smokers and exclusion of individuals with low certainty of type 2 diabetes (Supplementary Table 7 of Supplementary File 1). There was no association between leisure-time PA and mortality in 5857 British adults who performed at least a single 24-h dietary recall. Descriptive characteristics of adults with active transportation or occupations are shown in Supplementary Tables 8 and 9 of Supplementary File 1; their associations with outcomes are presented in Supplementary Tables 10 and 11 of Supplementary File 1.

4. Discussion

The main finding was that PA below and at contemporary recommendations was associated with lower all-cause and cardiovascular mortality in British and Chinese adults with type 2 diabetes, but these reductions were uncertain and inconsistent across cohorts. There was no association between PA and risk of major adverse cardiovascular events in the China Kadoorie Biobank, and activity equivalent to 90 min of walking or 38 min of strenuous sports per day, which far exceeds the WHO recommended level, was needed to lower the risk in the UK Biobank.

4.1. Comparison with other studies

Previous meta-analyses of the dose−response association between PA and mortality in adults with type 2 diabetes have been inconclusive. One suggested a weak, linear dose−response association[12] while the other provided some support for a curvilinear pattern, with a steeper gradient at low activity and diminishing returns at higher levels of activity.[14] None of these meta-analyses provided estimates directly applicable to the WHO's quantitative recommendations of 150−300 min of moderate-to-vigorous PA/week,[5] and the

Table 1
Descriptive characteristics.

Cohorts and characteristics	No leisure-time PA	Leisure-time PA below recommendation	Leisure-time PA at recommendation	Leisure-time PA above recommendation
UK Biobank (n = 14,913)				
Women	1391 (47.0)	5775 (41.2)	2956 (37.3)	4791 (29.2)
Age (year)	58.2 ± 7.3	59.1 ± 7.3	59.7 ± 7.2	60.3 ± 7.1
Body mass index (kg/m^2)	33.3 ± 6.6	31.6 ± 5.7	30.6 ± 5.3	29.9 ± 5.0
LTPA (MET-h/week)	0.0 ± 0.0	3.2 ± 2.1	10.8 ± 2.1	36.8 ± 26.7
Participation in sports	0 (0.0)	36 (0.6)	93 (3.1)	594 (12.4)
Duration of diabetes (year)	5.4 ± 7.2	5.1 ± 6.6	5.1 ± 6.7	5.4 ± 7.1
Education				
No qualifications	392 (28.2)	1278 (22.1)	542 (18.3)	901 (18.8)
Other qualifications than college/university degree	691 (49.7)	2986 (51.7)	1471 (49.8)	2418 (50.5)
College/university degree	308 (22.1)	1511 (26.2)	943 (31.9)	1472 (30.7)
Townsend index	0.4 ± 3.5	−0.7 ± 3.3	−1.1 ± 3.1	−1.4 ± 3.0
Smoking				
Never	685 (49.2)	2885 (50.0)	1498 (50.7)	2255 (47.1)
Former	514 (37.0)	2273 (39.4)	1203 (40.7)	2120 (44.2)
Current	192 (13.8)	617 (10.7)	255 (8.6)	416 (8.7)
Family history of CVD, cancer, or diabetes (yes)	1194 (85.8)	4910 (85.0)	2520 (85.3)	4069 (84.9)
Statins (yes)	881 (63.3)	3649 (63.2)	1934 (65.4)	3067 (64.0)
Use of blood pressure-lowering drugs				
0	718 (51.6)	3303 (57.2)	1738 (58.8)	2932 (61.2)
1	366 (26.3)	1393 (24.1)	689 (23.3)	1097 (22.9)
2	223 (16.0)	814 (14.1)	418 (14.1)	554 (11.6)
3 or more	84 (6.0)	265 (4.6)	111 (3.8)	208 (4.3)
Doctor diagnosis or on treatment for type 2 diabetes (yes)[a]	1101 (79.2)	4578 (79.3)	2405 (81.4)	3921 (81.8)
Use of blood glucose-lowering drugs[b]				
None	270 (24.5)	1263 (27.6)	801 (33.3)	1316 (33.6)
Insulin only	53 (4.8)	190 (4.2)	115 (4.8)	204 (5.2)
Non-insulin only	683 (62.0)	2756 (60.2)	1330 (55.3)	2136 (54.5)
Insulin and non-insulin	95 (8.6)	369 (8.1)	159 (6.6)	265 (6.8)
China Kadoorie Biobank (n = 17,457)				
Women	9523 (61.7)	616 (53.4)	1186 (54.3)	6132 (60.3)
Age (year)	55.4 ± 9.7	56.8 ± 9.6	58.7 ± 9.4	61.2 ± 8.4
Body mass index (kg/m^2)	25.5 ± 3.5	25.5 ± 3.3	25.3 ± 3.2	25.3 ± 3.2
LTPA (MET-h/week)	0.0 ± 0.0	5.3 ± 1.6	11.7 ± 1.8	35.9 ± 19.2
Participation in heavy PA/exercise[c]	1002 (10.5)	53 (8.6)	147 (12.4)	803 (13.1)
Duration of diabetes (year)	2.6 ± 4.2	3.5 ± 4.9	3.5 ± 4.7	4.2 ± 5.3
Education				
No school or primary school	4831 (50.7)	230 (37.3)	449 (37.9)	2327 (37.9)
Middle school	2609 (27.4)	201 (32.6)	366 (30.9)	1849 (30.2)
High school or higher	2083 (21.9)	185 (30.0)	371 (31.3)	1956 (31.9)
Smoking				
Never	6179 (64.9)	338 (54.9)	707 (59.6)	4078 (66.5)
Occasional	431 (4.5)	37 (6.0)	75 (6.3)	341 (5.6)
Former	637 (6.7)	64 (10.4)	129 (10.9)	696 (11.4)
Current	2276 (23.9)	177 (28.7)	275 (23.2)	1017 (16.6)
Family history of CVD, cancer, or diabetes (yes)	4524 (47.5)	319 (51.8)	617 (52.0)	2952 (48.1)
Statins (yes)	44 (0.5)	2 (0.3)	6 (0.5)	20 (0.3)
Use of blood pressure-lowering drugs				
0	8662 (91.0)	550 (89.3)	1055 (89.0)	5243 (85.5)
1	753 (7.9)	56 (9.1)	119 (10.0)	784 (12.8)
2 or more	108 (1.1)	10 (1.6)	12 (1.0)	105 (1.7)
Doctor diagnosis or on treatment for type 2 diabetes (yes) [a]	4379 (46.0)	337 (54.7)	701 (59.1)	3810 (62.1)
Use of blood glucose-lowering drugs[b]				
None	1637 (37.4)	118 (35.0)	243 (34.7)	1293 (33.9)
Insulin only	360 (8.2)	42 (12.5)	72 (10.3)	423 (11.1)
Chlorpropamide or metformin only	2282 (52.1)	167 (49.6)	375 (53.5)	2014 (52.9)
Insulin and chlorpropamide or metformin	100 (2.3)	10 (3.0)	11 (1.6)	80 (2.1)

Notes: Data are presented as n (%) or mean ± SD. Categories of leisure-time PA defined as: none (0 MET-h/week), below recommendation (>0−7.49 MET-h/week), at recommendation (7.5−14.9 MET-h/week), and above recommendation (≥15 MET-h/week). Percentages add up not to 100% due to rounding.

[a] Individuals with type 2 diabetes identified from self-report or use of glucose-lowering drugs (Eastwood et al.,[19] UK Biobank) or from self-reported diagnosis of diabetes from a doctor (China Kadoorie Biobank).

[b] Individuals identified with type 2 diabetes solely from measured HbA1c (UK Biobank) or random blood glucose (China Kadoorie Biobank) are not included in the denominator.

[c] Includes activities during work, transportation, domestic, and leisure activities.

Abbreviations: CVD = cardiovascular disease; HbA1c = hemoglobin A1c; LTPA = leisure-time physical activity; MET = metabolic equivalent; PA = physical activity.

Table 2
Leisure-time physical activity and all-cause mortality and cardiovascular disease.

	No leisure-time PA	Leisure-time PA below recommendation	Leisure-time PA at recommendation	Leisure-time PA above recommendation
All-cause mortality				
UK Biobank (n = 14,913; deaths = 1571)	1391/162	5775/610	2956/306	4791/493
Crude incidence rate/1000 person-years	12.8 (10.9−14.9)	11.5 (10.6−12.5)	11.3 (10.1−12.7)	11.3 (10.3−12.3)
Model 1 (HR (95%CI))	1 (reference)	0.80 (0.67−0.95)	0.73 (0.60−0.88)	0.65 (0.55−0.78)
Model 2 (HR (95%CI))	1 (reference)	0.90 (0.75−1.04)	0.84 (0.69−1.02)	0.78 (0.65−0.94)
Model 3 (HR (95%CI))	1 (reference)	0.94 (0.79−1.12)	0.90 (0.74−1.10)	0.85 (0.70−1.02)
Model 4 (HR (95%CI))	1 (reference)	0.96 (0.80−1.14)	0.93 (0.77−1.13)	0.87 (0.72−1.05)
China Kadoorie Biobank (n = 17,457; deaths = 2357)	9523/1232	616/74	1186/169	6132/882
Crude incidence rate/1000 person-years	19.2 (18.2−20.3)	18.5 (14.7−23.2)	21.6 (18.6−25.1)	21.5 (20.1−23.0)
Model 1 (HR (95%CI))	1 (reference)	0.86 (0.68−1.09)	0.82 (0.70−0.96)	0.69 (0.63−0.75)
Model 2 (HR (95%CI))	1 (reference)	0.87 (0.68−1.10)	0.88 (0.75−1.03)	0.77 (0.70−0.85)
Model 3 (HR (95%CI))	1 (reference)	0.87 (0.68−1.10)	0.88 (0.74−1.03)	0.77 (0.70−0.85)
Model 4 (HR (95%CI))	1 (reference)	0.86 (0.68−1.09)	0.88 (0.75−1.03)	0.77 (0.70−0.85)
Cardiovascular mortality				
UK Biobank (n = 14,913; deaths = 392)	1391/50	5775/154	2956/73	4791/115
Crude incidence rate/1000 person-years	3.9 (3.0−5.2)	2.9 (2.5−3.4)	2.7 (2.1−3.4)	2.6 (2.2−3.2)
Model 1 (sHR (95%CI))	1 (reference)	0.67 (0.49−0.92)	0.58 (0.40−0.83)	0.51 (0.36−0.71)
Model 2 (sHR (95%CI))	1 (reference)	0.75 (0.55−1.04)	0.68 (0.47−0.98)	0.61 (0.43−0.86)
Model 3 (sHR (95%CI))	1 (reference)	0.80 (0.58−1.11)	0.75 (0.52−1.09)	0.69 (0.48−0.97)
Model 4 (sHR (95%CI))	1 (reference)	0.83 (0.60−1.15)	0.79 (0.54−1.15)	0.72 (0.51−1.03)
China Kadoorie Biobank (n = 17,457; deaths = 1060)	9523/547	616/39	1186/83	6132/391
Crude incidence rate/1000 person-years	8.5 (7.8−9.3)	9.7 (7.1−13.3)	10.6 (8.5−13.1)	9.5 (8.6−10.5)
Model 1 (sHR (95%CI))	1 (reference)	1.04 (0.75−1.45)	0.93 (0.74−1.17)	0.70 (0.61−0.80)
Model 2 (sHR (95%CI))	1 (reference)	1.06 (0.76−1.48)	1.01 (0.80−1.28)	0.79 (0.69−0.92)
Model 3 (sHR (95%CI))	1 (reference)	1.06 (0.76−1.47)	1.01 (0.80−1.28)	0.79 (0.69−0.92)
Model 4 (sHR (95%CI))	1 (reference)	1.06 (0.76−1.48)	1.01 (0.80−1.28)	0.79 (0.68−0.91)
Major adverse cardiovascular events				
UK Biobank (n = 14,320; events = 2345)	1322/221	5550/948	2857/443	4591/733
Crude incidence rate/1000 person-years	20.1 (17.6−23.0)	20.6 (19.3−22.0)	18.6 (16.9−20.4)	19.1 (17.7−20.5)
Model 1 (sHR (95%CI))	1 (reference)	0.96 (0.83−1.11)	0.83 (0.70−0.97)	0.79 (0.68−0.92)
Model 2 (sHR (95%CI))	1 (reference)	1.02 (0.88−1.18)	0.90 (0.77−1.07)	0.87 (0.74−1.02)
Model 3 (sHR (95%CI))	1 (reference)	1.07 (0.92−1.24)	0.97 (0.82−1.15)	0.94 (0.80−1.11)
Model 4 (sHR (95%CI))	1 (reference)	1.10 (0.94−1.27)	1.00 (0.85−1.19)	0.98 (0.84−1.15)
China Kadoorie Biobank (n = 16,127; events = 4458)	8931/2211	569/154	1076/303	5551/1790
Crude incidence rate/1000 person-years	40.5 (38.9−42.6)	46.6 (39.8−54.6)	47.3 (42.3−53.0)	55.8 (53.2−58.4)
Model 1 (sHR (95%CI))	1 (reference)	1.10 (0.90−1.30)	1.00 (0.89−1.13)	1.06 (1.00−1.13)
Model 2 (sHR (95%CI))	1 (reference)	1.01 (0.86−1.19)	0.92 (0.82−1.04)	0.96 (0.89−1.03)
Model 3 (sHR (95%CI))	1 (reference)	1.01 (0.86−1.19)	0.93 (0.82−1.05)	0.97 (0.90−1.04)
Model 4 (sHR (95%CI))	1 (reference)	1.01 (0.86−1.19)	0.93 (0.82−1.05)	0.96 (0.89−1.03)

Notes: Categories of leisure-time PA defined as: none (0 MET-h/week), below recommendation (>0−7.49 MET-h/week), at recommendation (7.5−14.9 MET-h/week), and above recommendation (≥15 MET-h/week).
Model 1: adjusted for sex and age (timescale).
Model 2: Multivariable-adjusted.
UK Biobank: Model 1 + education (no qualifications, qualifications, not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current <3 times/week, current >3 times/week), diet quality index (0, 1, 2−3), body mass index (continuous), family history of diabetes, cardiovascular disease, or cancer (yes/no), inclusion method (self-reported type 2 diabetes/use of medication or biochemistry), depression (yes/no), loneliness (yes/no), diabetes duration (continuous).
China Kadoorie Biobank: Model 1 + education (no school or primary school, middle school, high school or higher), household income (<RMB10,000/year, ≥RMB10,000−19,999/year, ≥RMB20,000−34,999/year, ≥RMB35,000/year), marital status (married, yes/no), has health coverage (yes/no), employment (sedentary, standing, manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, occasional, former regular, current), alcohol intake (never/occasionally, former weekly, current <3 days/week, current ≥3 days/week), regular fruit consumption (≥4 days/week, yes/no), regular meat consumption (≥4 days/week, yes/no), body mass index, (continuous), family history of diabetes, cardiovascular disease, or cancer (yes/no), inclusion method (self-reported type 2 diabetes/use of medication or biochemistry), experienced food shortage with weight loss (yes/no), major depression in last 12 months (yes/no), diabetes duration (continuous).
Model 3 (main model): Model 2 + adjustment for body mass index.
Model 4: Model 3 + adjustment for use of glucose-lowering drugs, statins, and blood-pressure-lowering drugs.
Abbreviations: 95%CI = 95% confidence interval; HR = hazard ratio; MET = metabolic equivalent; PA = physical activity; sHR = subdistribution hazard ratio.

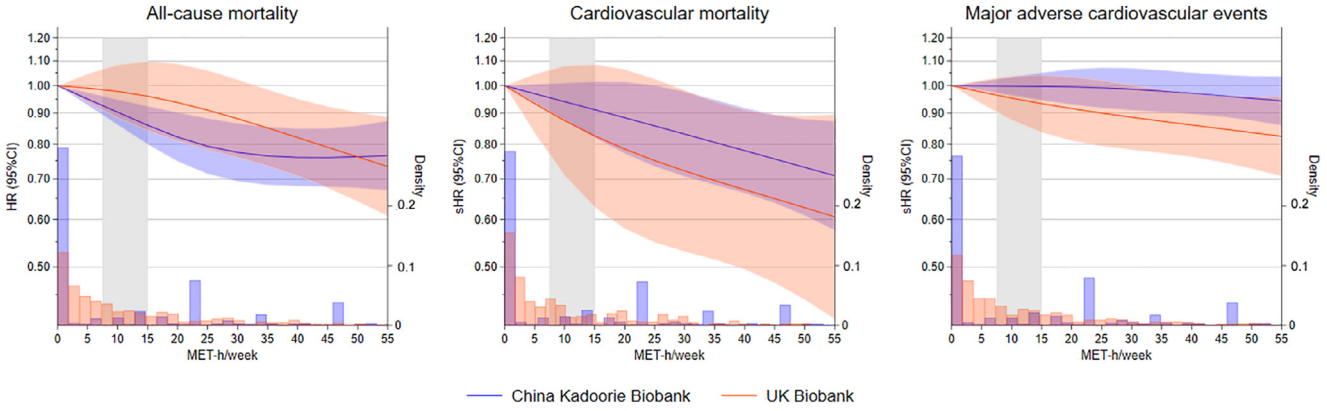

Fig. 1. Dose−response associations between leisure-time PA and all-cause mortality and cardiovascular disease. Solid lines are HRs or subdistribution HRs (based on Model 3) with 95%CI in shaded areas. Vertical shaded area is recommended level of PA. Knot locations are 2, 10, and 41 MET-h/week (UK Biobank) and 10, 23, and 53 MET-h/week (China Kadoorie Biobank). Dose−response curves are truncated at 55 MET-h/week to maintain data overlap between the cohorts. *p* for non-linearity (all-cause mortality) = 0.51 (UK Biobank) and 0.03 (China Kadoorie Biobank). *p* for non-linearity (cardiovascular mortality) = 0.69 (UK Biobank) and 0.97 (China Kadoorie Biobank). *p* for non-linearity (major adverse cardiovascular events) = 0.77 (UK Biobank) and 0.61 (China Kadoorie Biobank). 95%CI = 95% confidence interval; HR = hazard ratio; MET = metabolic equivalent; PA = physical activity; sHR = subdistribution hazard ratio.

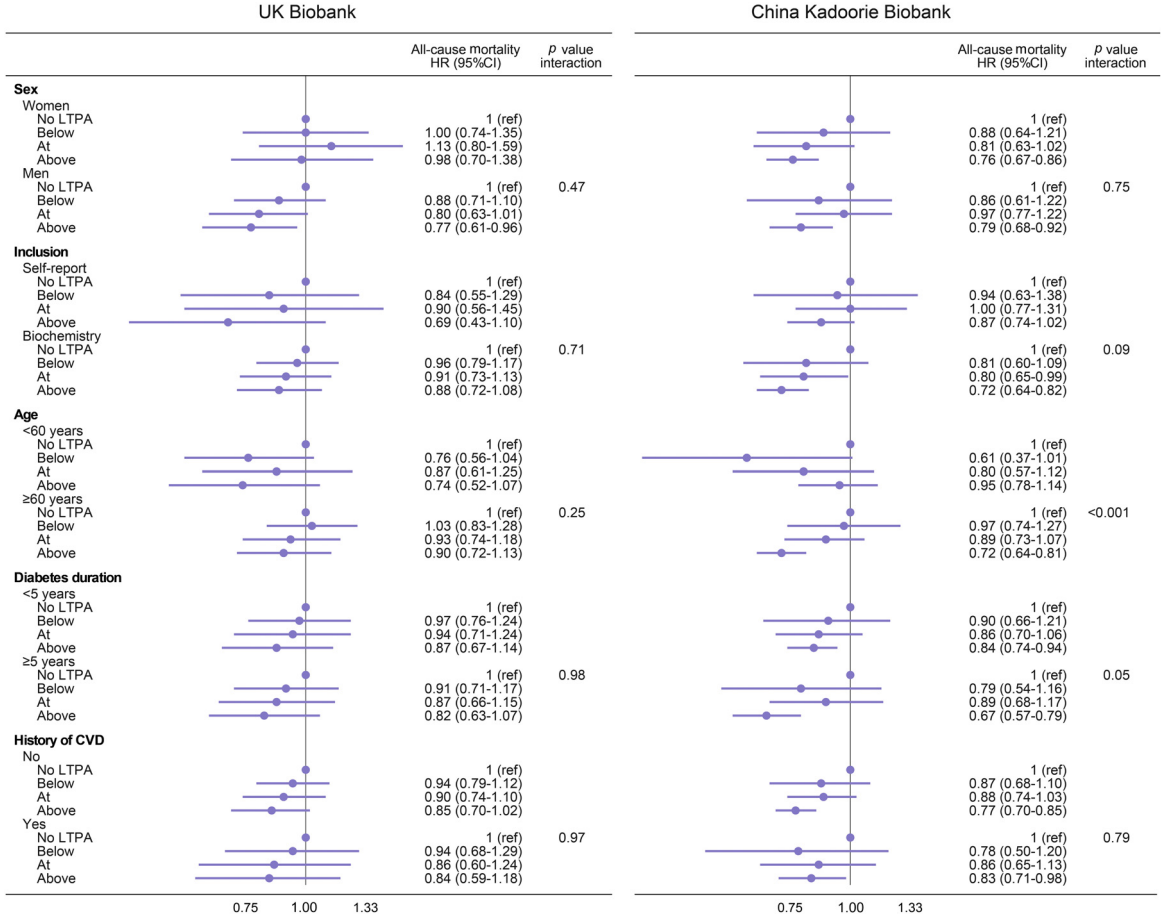

Fig. 2. Leisure-time PA and all-cause mortality by participant characteristics. HRs (based on Model 3) with 95%CI. No LTPA: 0 MET-h/week; Below: below recommendation (>0−7.49 MET-h/week); At: recommended levels (7.5−14.9 MET-h/week); Above: above recommendation (≥15 MET-h/week). *p* value for interaction from likelihood ratio test. Interaction with age examined by setting time-on-study as the timescale, including an indicator for above *vs.* below sixty years old, and an interaction term between the age-indicator and leisure-time PA. Estimates for participants with no history of CVD are from main analysis, included for comparison. Numbers of participants (deaths) in UK Biobank are: women (5538 (439)), men (9375 (1132)), included from self-report (12,005 (1310)), included from biochemistry (2908 (261)), <60 years of age (6617 (350)), ≥60 years of age (8296 (1221)), diabetes duration <5 years (9185 (820)), diabetes duration ≥5 years (5728 (751)), no history of CVD (14,913 (1573)), and a history of CVD (2028 (445)). Numbers of participants (deaths) in China Kadoorie Biobank are: women (10,547 (1321)), men (6910 (1036)), included from self-report (9227 (1420)), included from biochemistry (8230 (937)), <60 years of age (10,123 (658)), ≥60 years of age (7334 (1699)), diabetes duration <5 years (13,037 (1562)), diabetes duration ≥5 years (4420 (795)), no history of CVD (17,457 (2357)), and a history of CVD (2952 (771)). CVD = cardiovascular disease; HR = hazard ratio; LTPA = leisure-time physical activity; MET = metabolic equivalent; PA = physical activity.

evidence has low certainty according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria.[12] A very strong curvilinear dose−response association was observed in a study of 3000 British adults with type 2 diabetes. Compared with no activity, activity below the recommended level was associated with 26% lower mortality, and meeting recommendations was associated with 35% lower mortality.[27] Similarly, in an East Asian cohort, PA below and at the recommended level was associated with 32% and 37% lower mortality, respectively.[28] In both studies, a similar curvilinear dose−response pattern was observed for cardiovascular mortality. This pattern and effect sizes are consistent with data from the general population.[29,30] In our study, PA below the recommended level had a much weaker association with mortality outcomes. The all-cause mortality risk reduction was 6% in the UK Biobank and 13% in the China Kadoorie Biobank, but cardiovascular mortality was 6% higher in the China Kadoorie Biobank. PA below recommendations was associated with 20% lower cardiovascular mortality in the UK Biobank, but there was no support of a curvilinear dose−response association. Compared with our study, the East Asian cohort was based on long-term average PA from several repeated assessments, demonstrating that sustained engagement in PA is needed to maximize health benefits. The study based in the UK was much smaller in comparison to ours and included a less comprehensive approach to minimize confounding. Collectively, our data corroborate previous evidence that adults with type 2 diabetes could achieve important reductions in total and cardiovascular mortality from leisure-time PA but suggest that larger amounts than currently recommended are needed to achieve those benefits.

PA, including exercise, improves conventional cardiovascular risk markers, including HbA1c, in adults with type 2 diabetes.[5] Effects are dose-dependent with a mean change in HbA1c of −0.36% with structured weekly exercise of 150 min or less and −0.89% with more than 150 min per week.[31] However, translating these effects into hard end-points, such as mortality and cardiovascular events, have been far less convincing. The LOOK AHEAD trial compared a weight-loss and PA-based lifestyle intervention (aiming for 175 min of moderate-intensity activities per week) with usual care but found no reduction in cardiovascular morbidity or mortality.[32] In the Nurses' Health Study and the Health Professionals Follow-up Study, PA was not associated with non-fatal stroke, coronary heart disease, or myocardial infarction[33] and more than 4 h of exercise per week was needed to lower a composite of fatal and non-fatal CVD.[33,34] These results are consistent with our findings and suggest PA does not lower rates of non-fatal CVD in adults with type 2 diabetes but may instead prevent cardiovascular mortality by increasing survival with CVD.

4.2. Cross-country comparison

We were unable to determine a consistent minimal effective dose or a maximal achievable risk reduction across both cohorts and mortality outcomes. Any non-zero level of PA was associated with lower all-cause mortality in the China Kadoorie Biobank, whereas the dose−response pattern was initially modest and shallow in the UK Biobank. Conversely, the dose−response association with cardiovascular mortality was noticeably steeper in British than in Chinese adults. A maximal achievable all-cause mortality reduction of 23% was observed at approximately 35 MET-h/week in Chinese adults, but no upper level of benefit was observed for other outcomes in either cohort.

Several factors could explain these differences. The large number of participants with undiagnosed type 2 diabetes from China reflects different health-care systems, which could also impact detection and coding of cardiovascular outcomes. Similarly, the difference in the use of cardiovascular prophylactics is reflected in the CVD incidence rates. The UK Biobank and China Kadoorie Biobank cohorts are subject to different selection-mechanisms, with a particularly high risk of healthy-volunteer bias in the UK Biobank.[35] In high-income Western countries, BMI is strongly linked to a suite of lifestyle risk factors and with poorer socioeconomic circumstances.[36] These pervasive sources of confounding are expected to amplify associations between PA and mortality, and residual confounding may remain despite careful statistical modeling.[16] In contrast, there was no gradient in BMI across leisure-time PA in the China Kadoorie Biobank, implying that BMI and its associated network of socioeconomic factors are not a source of confounding in this context. The minimal attenuation of effect sizes after adjustment for BMI in the China Kadoorie Biobank confirms this notion and suggests the association between PA and all-cause and cardiovascular mortality is independent of BMI. Finally, adults of Asian origin may have a distinct pathophysiology and develop type 2 diabetes at a lower BMI compared with adults of European origin.[37] Our data thus provide much-needed representation of the majority of adults living with type 2 diabetes worldwide.

4.3. Strengths and weaknesses

We included large population-based samples, and we therefore expect participants to represent the level of variation in social conditions and medical treatment given to the majority of adults with type 2 diabetes in the UK and China. Our statistical model was informed by a directed acyclic graph to reduce the impact of confounding, and we carefully removed participants with mobility limitations or a history of major conditions other than type 2 diabetes in addition to left-censoring the first 3 years of follow-up to reduce confounding from poor health. Corroborative analysis in patients with type 2 diabetes and a history of CVD provides wider generalizability to a common high-risk group. We highlight the following limitations: (a) Despite our best efforts to standardize data analysis between the 2 studies, the leisure-time PA questionnaires were not identical. Specifically, only the main type of activity was reported in the China Kadoorie Biobank, which could underestimate absolute levels of PA in individuals performing multiple activities and, thereby, influence the dose−response pattern. Additionally, we included light do-it-yourself activities (assigning these as 2.25 METs) from the UK Biobank questionnaire

while there were no named light intensity activities in the questionnaire given to the Chinese cohort. Light intensity physical activities likely also contribute to lower mortality risk[5,10] but are not included in current quantitative PA recommendations. We included light do-it-yourself activities because this was 1 of 5 named leisure activity categories. The median contribution, among those reporting any, was 2.1 MET-h/week. (b) Self-reported PA is imprecisely measured. When PA is assessed by devices, the magnitude of associations with mortality outcomes tend to be much stronger, and the maximal risk reduction is observed at lower absolute levels of activity.[38,39] In addition, we accounted for non-leisure-time PAs by adjustment based on categorical variables, which may leave residual bias. Large observational studies with device-measured total PA will provide more robust quantifications of the dose−response relationship and the minimal amount of PA needed to prevent major health outcomes in adults with type 2 diabetes.[40] (c) There was no association between leisure-time PA and mortality in the subsample of UK Biobank participants with repeated dietary recalls ($n = 5857$), which may indicate residual confounding from diet quality or quantity. However, this subsample may also represent a highly selected and motivated group, which can lead to bias in observational studies of aetiology.[41] Finally, as an observational study, residual confounding and other biases may also impact the observed dose−response relationships.

5. Conclusion

The PA recommendations given by the WHO and the American Diabetes Association are quantitatively identical to general population guidelines.[10] Our study provides little empirical support for such universal guidelines and messaging, suggesting a tailored PA recommendation may be appropriate for adults with type 2 diabetes.

Leisure-time PA was inversely associated with all-cause and cardiovascular mortality in British and Chinese adults, but the magnitude of the associations was small and inconsistent with activity corresponding to contemporary PA recommendations for adults with type 2 diabetes. The dose−response association was steeper for death from cardiovascular causes than for all-cause mortality in British adults while the opposite pattern was observed in Chinese adults. Very high levels of PA were associated with lower rates of major adverse cardiovascular events in British adults but not in Chinese adults.

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Authors' contributions

JT conceived and designed the study, performed the statistical analysis, and drafted the first version of the manuscript; ML curated parts of the data, interpreted the results, and critically revised the manuscript; MASL, KED, BdPC, MRL, RWT, UE, and DD conceived and designed the study, interpreted the results, and critically revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

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Data availability statement

This manuscript was prepared based on data available to Bona Fide researchers. Application for UK Biobank data can be made here: https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. Application for China Kadoorie Biobank data can be made here: https://www.ckbiobank.org/data-access.

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2023.10.004.

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