Physical activity and diabetes mortality in people with Type 2 Diabetes: A Prospective Cohort Study of 0.5 Million US people

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ABSTRACT

AIM: To examine the association between physical activity and the cause of death with the greatest risk related to type 2 diabetes in a large population-based cohort representative of the general US adult population.

METHODS: A total of 41,726 adults suffering from type 2 diabetes (62±14 years) and 459,660 adults without diabetes (46±18 years) who participated in the National Health Interview Survey from 1997 to 2014 were included in this prospective cohort study. Self-reported moderate-to-vigorous physical activity (MVPA) was and categorized into inactive, insufficiently active, active and very active. Mortality data was obtained from the National Death Index. Cox regression models adjusted for potential confounders were performed to estimate hazard ratios (HR) and 95% Confidence Intervals (CI).

RESULTS: Diabetes mortality cause showed the highest relative risk of death among adults with type 2 diabetes compared to adults without diabetes (HR=5.72; 95%CI:3.15-10.39). There was a non-linear inverse dose-response association between MVPA and diabetes mortality among adults with type 2 diabetes, up to a plateau in risk reduction at approximately 500 min/week. Any level of activity was inversely associated with a significantly lower risk of diabetes mortality compared to being inactive (insufficiently active HR[95%CI]=0.71:0.54-0.97, active HR[95%CI]=0.68:0.49-0.95, very active HR[95%CI]=0.44:0.32-0.60). Compared to adults without diabetes, the risk of diabetes mortality decreased from HR[95%CI]=7.38[4.00-13.58] for inactive people with 2 type diabetes to HR[95%CI]=3.34[1.76-6.32] for very active people with type 2 diabetes.

CONCLUSIONS: Higher levels of MVPA were associated with lower risk of diabetes mortality among adults with type 2 diabetes.

KEYWORDS: diabetes, mortality, adults, physical activity, prevention.

INTRODUCCIÓN

Diabetes represents a major global health concern that affected 463 million people worldwide in 2019 (representing the 9.3% of total adult population), and its prevalence is projected to continue rising in the coming years [1]. In 2019, 34.1 million United States (US) adults had diabetes (13%) [2], ranking the 3rd country worldwide for the number of adults with diabetes. Given the increasing prevalence of diabetes, and the mortality and economic burden associated [3–5], it is important to investigate if modifiable lifestyle factors might be important for secondary prevention strategies, mainly for type 2 diabetes which represents over 90% cases of diabetes.

Previous research indicates that physical activity promotion might be important in these public health strategies since high amounts of physical activity have been inversely associated with the risk of all-cause and cardiovascular disease mortality in adults with diabetes [6] and, specifically, with type 2 diabetes [7]. Although cardiovascular disease has been traditionally considered to be the main cause of death among adults with diabetes [8], recent data suggested that the number of non-vascular deaths in adults with diabetes has increased in the US and other countries, leading to a diversification of forms of diabetes-related mortality [8,9]. Indeed, the disease course of diabetes leads to multiple health complications as consequence of blood hyperglycemia and hyper-insulinemia, among other causes, which ultimately increase the risk of mortality [10]. Interestingly, previous studies showed that physical activity is able to improve these pathophysiological factors of diabetes through different mechanisms that contribute to metabolic regulation and blood glucose control [11,12].

Since the cause of death with the greatest risk among people with type 2 diabetes could be considered a long-term indicator of disease progression, understanding the role of physical activity on this relationship may have important implications for public health and clinical therapeutic measures at population level. The aim of this study was to examine the association between physical activity and the cause of death with the greatest risk related to type 2 diabetes in a large population-based cohort representative of the general US adult population.

METHODS

Study population

The present study analyzed data from the National Health Interview Survey (NHIS), a nationally representative survey of the civilian non-institutionalized US population. Household interviews are conducted annually by the Centers for Disease Control and Prevention from the National Center for Health Statistics via the US Census Bureau. Participants are selected using a stratified, multistage area probability design. One adult and one child are selected randomly from each household for a detailed interview on the health status, health-care access, and health behaviors. Participants provided informed consent before participation in the study. The National Center for Health Statistics ethics review board approved the NHIS, and the present study is based on secondary analyses of de-identified NHIS data publicly available, which did not require additional approval from the institutional review board. Detailed information on the design and methodology can be found elsewhere [13].

This study included representative adult data from 18 cross-sectional waves conducted from 1997 to 2014. Of the total NHIS sample recorded during this period (n=1,710,059), 529,363 adults were eligible for mortality follow-up. A total of 504,028 participants remained as eligible study participants in our analyses after excluding participants without complete data on diabetes status (n=3262) and physical activity (n=22,073). Diabetes status was defined as to have ever been diagnosed with diabetes by a doctor or as to be taking glucose-lowering medication at baseline. Among the analytic sample, 2543 participants with possible type 1 diabetes (defined by use of insulin and age at diabetes onset <30 years) [8] and 99 women with gestational diabetes were excluded, remaining 41,726 participants suffering from type 2 diabetes and 459,660 participants who did not have diabetes at baseline (Supplemental figure 1).

Physical activity

Participants self-reported the frequency and duration of leisure-time physical activity by answering two set of questions: (1) Frequency of light or moderate intensity physical activity (MPA): "How often do you do light or moderate leisure-time physical activities for at least 10 minutes that cause only light sweating or a slight to moderate increase in breathing or heart rate?" Duration: "About how long do you do these light or moderate leisure-time physical activities each time?". (2) Frequency of vigorous physical activity (VPA): "How often do you do vigorous leisure-time physical activities for at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate?" Duration: "About how long do you do these vigorous leisure-time physical activities each time?".

The total amount of MPA and VPA was calculated by multiplying duration (minutes per week) and frequency (times per week). Total minutes per week of leisure-time moderate-to-vigorous physical activity (MVPA) were calculated accounting for intensity [14] as follows: MPA + [2 x VPA] (both in minutes per week). Weekly MVPA was categorized into 0 min/week (inactive), 0.1 to 149 min/week (insufficiently active), 150 to 300 min (active), >300 min (very active). The active cut point was based on the recently updated WHO physical activity recommendations [15]. MVPA was truncated to 1680 min/week due to sparse data [16].

Mortality

Mortality outcomes were determined according to the National Death Index records. The causes of death were determined using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes (ICD-10) [17]. The mortality outcomes investigated to test the cause of death with the greatest risk related to type 2 diabetes were all cause, cardiovascular disease (I09, I11, I13, I20-I51, I60-I69), cancer (C00-C97), diabetes mellitus (E10-E14), Alzheimer's disease (G30), kidney disease (N00-N07, N17-N19, N25-N27) and other causes. Follow-up duration was determined as the time in months from the beginning of the NHIS participation to death for decedents or to the censoring date (31 December 2015) for survivors.

Study covariates

Socio-demographic variables included age (years), sex (men; women), race (Hispanic; non-Hispanic White; non-Hispanic Black; and others), marital status (married or living with partner; divorced, separated or widowed; and never married), and education level (less than high school degree; high school degree; and more than high school degree). Lifestyle risk factors included smoking status (never; former; and current), alcohol drinking status (never; former; and current), and body mass index calculated as weight in kilograms divided by height in meters squared using self-reported weight and height and categorized as non-overweight/obesity (<25 kg/m^2), overweight (25 kg/m^2 to 29.9 kg/m^2), and obesity (≥30 kg/m^2). Clinical variables included self-reported history of hypertension (yes; no), cardiovascular disease including coronary heart disease and stroke (yes; no), cancer (yes; no), limitations of daily living activities (yes; no), diabetes duration (years since diagnose) and taking insulin or oral glucose-lowering medication status (yes; no).

Statistical analyses

Baseline characteristics of the study sample were summarized as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. Baseline differences across MVPA categories were examined using analysis of variance for continuous variables and $\chi 2$ tests for categorical variables.

To determine the risk of specific mortality in type 2 diabetes adults, Cox proportional hazards regression model was used to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), considering adults without diabetes as the reference group.

Cox regression models were also used to estimate HRs with corresponding 95% CIs testing the association between MVPA and diabetes mortality in adults with type 2 diabetes, with months of follow-up at the time scale. Firstly, to examine the dose–response relationship between MVPA (as continuous variable) and diabetes mortality, cubic spline Cox regression in a fully adjusted model was used with 3 knots placed at the 10th, 50th, and 90th percentiles. Secondly, Cox analysis was also used to estimate the risk of diabetes mortality across the four MVPA categories in type 2 diabetes adults, considering the inactive group (0 min/week) as the reference. Five models with sequential adjustment for potential confounders were created: model 1 included age, sex, ethnicity, marital status and educational level; model 2 included variables in model 1 plus smoking status, alcohol consumption and body mass index; model 3 additionally included suffering from the following chronic conditions: hypertension, cancer and cardiovascular disease; model 4 additionally included having limitations for activities of daily living; model 5 additionally included diabetes medication and diabetes duration. Since there was a small number of missing data on covariates (less than 3% in all covariates), the missing indicator approach was used for categorical covariates, which involves creating a dummy category to denote missing data. Additionally, fully adjusted Cox regression model was used to estimate the association between MVPA categories and the risk of diabetes mortality in the whole sample, considering adults without diabetes as the reference group.

Sensitivity analysis for the main analyses on the association between physical activity and diabetes mortality among people with diabetes were performed by removing participants with cardiovascular disease and cancer, with limitations of daily living activities, and who died within the first four years of follow-up to deal with the possible effect of reverse causation.

Potential interactions between each covariate and MVPA for diabetes mortality in adults with type 2 diabetes were tested by introducing the interaction term into separate Cox models (Wald test).

All analyses accounted for sample weights provided on the 2015 linked mortality data to prevent biased mortality estimates. Moreover, stratums, clusters, and weights were used in all data analyses to account for the complexity of survey designs and to assure generalization of the estimates [13]. Statistical significance was set at two-sided $P<0.05$. All data analyses were performed using STATA version 14.2 (Stata Corp, College Station, TX, USA).

RESULTS

Among the 41,726 adults suffering from type 2 diabetes, 55.3% were women, and 45.6% were older than 65 years (mean age, SD: 62 years, 13.7) (Table 1). Overall, they were more likely to be non-Hispanic White, married, with more than high school educational, never smokers and current alcohol drinkers. The prevalence of adults with type 2 diabetes being inactive, insufficiently active, active and very active was 53.1%, 19.7% 11.4 % and 15.8%, respectively. Adults with type 2 diabetes who were men, non-Hispanic White, married, with a higher educational level, with no smoking history and being current alcohol drinkers were more likely to report higher levels of MVPA. In addition, adults with type 2 diabetes in the most active group were less likely to have other chronic conditions or limitations in activities of daily living. Baseline characteristics of adults without diabetes (n=459,660) are shown in supplemental table 1.

Among adults suffering from type 2 diabetes, 11,176 deaths occurred during the 8.6-year median follow-up (ranging from 1 month to 18.4 years). Adults with type 2 diabetes were more likely to die from diabetes than those without diabetes (HR=5.72; 95% CI: 3.15 to 10.39;

p<0.001). Diabetes mortality cause showed the highest relative risk of death among adults with type 2 diabetes (table 2), and this association was observed from the beginning of the follow-up (supplemental figure 2).

After statistical adjustment, we found a non-linear (P<.001 for non-linear component) inverse dose-response association between MVPA and diabetes mortality among adults with type 2 diabetes (figure 1), with a plateau in risk reduction at high levels of activity (approximately at 500 min/week). The multivariate adjusted models across MVPA categories reported in table 3 indicated that in adults with type 2 diabetes any level of activity was inversely associated with a significantly lower risk of diabetes mortality compared to performing 0 min/week of MVPA. Specifically, the full adjusted model showed 29% lower risk of diabetes mortality in insufficiently active adults (HR=0.71; 95% CI: 0.54 to 0.97), 32% lower risk in active adults (HR=0.68; 95% CI: 0.49 to 0.95), and 56% lower risk in very active adults (HR=0.44; 95% CI: 0.32 to 0.60). The risk of diabetes mortality in adults with type 2 diabetes meeting the MVPA vs. not meeting recommendations was 42% lower (95%CI: 0.26 to 0.55); risk estimates were not significantly different when stratified by covariates (all P>.05) (supplemental table 2).

Adults with type 2 diabetes showed higher diabetes mortality risk than adults without diabetes at any level of activity; however, mortality risk decreased across MVPA categories in adults with type 2 diabetes compared to adults without diabetes (figure 2). Inactive adults with type 2 diabetes had the greatest diabetes mortality risk (HR=7.38; 95% CI: 4.00 to 13.58), whereas very active adults with type 2 diabetes had less than half this mortality risk (HR=3.34; 95% CI: 1.76 to 6.32).

In sensitivity analyses among participants with type 2 diabetes (supplemental table 3), the results were attenuated but showed similar association patterns after excluding participants with prevalent cardiovascular disease and cancer (n=20,690 individuals). Also, similar results were obtained after excluding participants with limitations of daily living activities (n=3108 individuals) and excluding people who died from diabetes during the first 4 years of follow-up (n=234 individuals).

DISCUSSION

Findings from this nationally representative cohort of US adults showed that physical activity was associated in a curvilinear inverse dose-response pattern with diabetes mortality in adults with type 2 diabetes, which was the mortality cause associated to the greatest risk of death in this population. This outcome has clinical and public health relevance because no threshold for the beneficial effect of physical activity on diabetes mortality was found. Thus, compared to being physically inactive, even low levels of physical activity were associated with lower risk of diabetes mortality, and the association was more marked at higher activity levels up to a plateau at about 500 min/week from which the dose–response curve flattened out.

Our results support previous studies carried out in US [18,19] and Asian population [20], which reported that adults with type 2 diabetes were at an increased risk of death from a wide range of diseases, with the highest relative risk for death due to diabetes itself. Thus, it is not surprising that diabetes appeared as the underlying cause of death on 83,564 death certificates in the US in 2017, being the seventh leading cause of death in this country [2]. Although reporting the cause of death on the death certificate according to international coding rules (i.e. ICD) can be sometimes complex [21], the reasons to code a death to diabetes as the underlying cause are usually direct consequences of diabetes disease (i.e. ketoacidosis or hyperosmolar coma) [22,23]. Indeed, fasting glucose levels was considered a directly relevant factor associated with increased mortality risk from several causes in patients with diabetes [24]. However, due to the fact that diabetes is a multisystem disorder related to increased risk of microvascular and microvascular conditions [25], deaths in people with diabetes are more usually coded to related complications such as stroke and ischaemic heart disease [21], leading to underestimation of diabetes as cause of death [21,26]. Yet, non-vascular conditions are emerging as leading causes of death in adults with diabetes among adults in US [8] and also in Europe [9], suggesting that specific death causes in people with diabetes require further investigation.

Our results add important data to the current literature about the association between physical activity and cause-specific mortality in adults with type 2 diabetes since diabetes is uncommonly investigated, possibly because large study sizes with a relatively large number of cases are needed to obtain precise estimates. The present study showed not only that higher physical activity levels were associated with lower risk of diabetes mortality in adults with type 2 diabetes, but also that it attenuated the risk of diabetes mortality in comparison to people without diabetes. These results are unique since for the first time the impact of physical activity on diabetes mortality in a representative sample of adults with type 2 diabetes was examined, limiting direct comparison with previous studies. Our findings support that daily physical activity is an accessible secondary prevention strategy [27] to reduce deaths from the mortality cause with greatest relative risk in adults with type 2 diabetes, which complements previous studies suggesting reduction in the risk of all-cause mortality [6].

We speculate that these results may reflect the direct benefits of physical activity on the pathological progression of diabetes caused by the decline in beta-cell function and insulin resistance [10]. For instance, physical activity increases the glucose uptake and utilization, contributing to blood glucose control [11,28], as a result of several adaptations like improved translocation of GLUT-4, and increased mitochondrial biogenesis, angiogenesis and muscle mass [29,30]. Moreover, physical activity is able to enhance insulin action in the target organs [28,31] and improve insulin secretion due to the protection of pancreatic β-cells function [12,32], possibly by reduction of pancreatic inflammation, oxidative stress injury in the tissues and lipid accumulation [33]. These physiological mechanisms driven by physical activity lead to multi-tissue adaptations [29,30], contributing to the reduction of both blood hyperglycemia and hyper-insulinaemia [34], which in turn may reduce over time the risk of direct causes related to diabetes mortality.

In light of the results of the current study and of previous data [35], daily physical activity practice should be encouraged among adults with type 2 diabetes. Recent guidelines state that all adults should engage in 150-300 minutes of moderate-intensity aerobic physical activity, or 75-150 min of vigorous-intensity activity, or an equivalent combination of both intensities, per week [15]. These recommendations are in line with specific recommendation for adults with type 2 diabetes, which established the same physical activity intensity thresholds [35]. Although our results showed a higher reduction of physical activity on diabetes-specific mortality at recommended levels, lower levels of physical activity appeared to be also beneficial to reduce diabetes mortality risk. This fact is in line with current international recommendations suggesting that any physical activity is better than none, and more physical activity is better for optimal health [36], which may be relevant for people with type 2 diabetes who would be unable or unwilling to participate in recommended physical activity duration (i.e. due to poor physical fitness or activity limitations).

This study has several strengths. Primarily, it included data from the NHIS, which provides the largest nationally representative cohort data with diagnosed diabetes to date. Moreover, it allowed to register data on diabetes mortality, which is a cause of death poorly investigated. In addition, including a representative group of adults of the population without type 2 diabetes as reference group for the analyses, increases the generalizability of the results. Despite these strengths, several limitations could be identified. Firstly, physical activity and diabetes history were self-reported, which might be susceptible to measurement error. Due to this issue, we were not able to capture adults with undiagnosed diabetes; thus, we cannot rule out that adults who were unaware of their condition were misclassified as adults without diabetes. Thirdly, physical activity was determined at a single point in time, implying that changes in this behavior over time were not accounted in the analyses, which might have underestimated the magnitude of the associations. Finally, although the analyses were adjusted for several potential confounders including socio-demographic, behavioral and clinical factors including weight status, residual and unmeasured confounding (e.g., dietary factors, glucose control, etc.) remain. For example, our results could be attenuated (i.e., mediator) or modified (i.e., moderator) if dietary patterns were included in the analyses due to its specific impact on glycemic control in patients with type 2 diabetes [34]; despite the fact we found consistent associations, our results must be interpreted with caution.

In conclusion, our results showed that among a representative sample of adults with type 2 diabetes, any amount of physical activity was inversely associated to the risk of diabetes-mortality. Our findings suggest that physical activity may directly benefit diabetes pathology progression reducing the cause of the death associated to the greatest risk of mortality in this population. These outcomes highlight the importance of promoting physical activity in people with type 2 diabetes in order to reduce the mortality burden associated to this chronic disease.

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Author Contributions

Study concept and design: M.R.B-V and D.M-S. Statistical analysis: M.R.B-V, D.M-S. and V.C-S. Analysis and interpretation of data: all authors. Drafting of the manuscript: M.R.B-V and D.M-S. Critical revision of the manuscript for important intellectual content: V.C-S, K.P.S, F.R-A and D.M-U. All authors have reviewed and approved the final manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Figure 1. Dose-response association between moderate-to-vigorous physical activity (MVPA) and diabetes mortality in people with type 2 diabetes. MVPA was truncated to 1680 min/week. Analyses were adjusted for age, sex, ethnicity, marital status, educational level, smoking status, alcohol consumption, body mass index, hypertension, cancer, cardiovascular disease, diabetes medication, diabetes duration and limitations for activities of daily living.

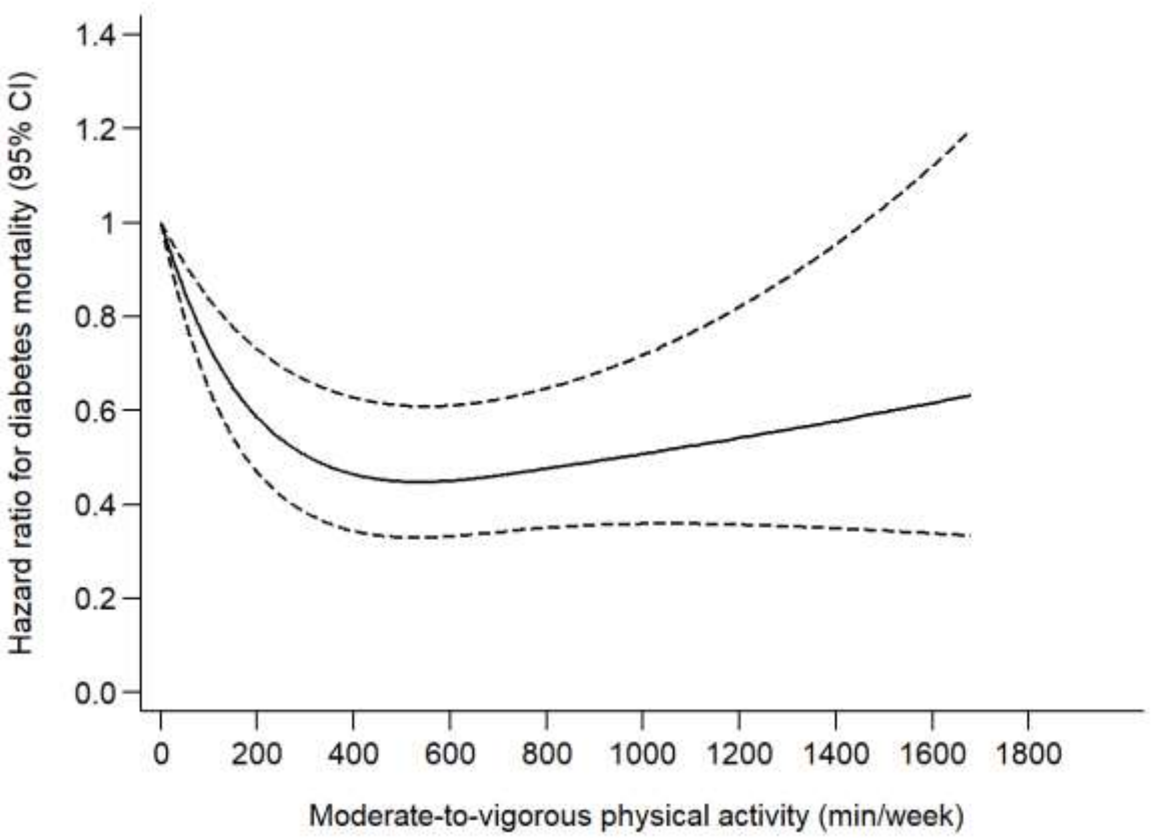

Figure 2. Risk of diabetes mortality in people with type 2 diabetes by moderate-to-vigorous physical activity (MVPA) categories. Reference category: people without type 2 diabetes. Analyses were adjusted for age, sex, ethnicity, marital status, educational level, smoking status, alcohol consumption, body mass index, hypertension, cancer, cardiovascular disease, diabetes medication, diabetes duration and limitations for activities of daily living.

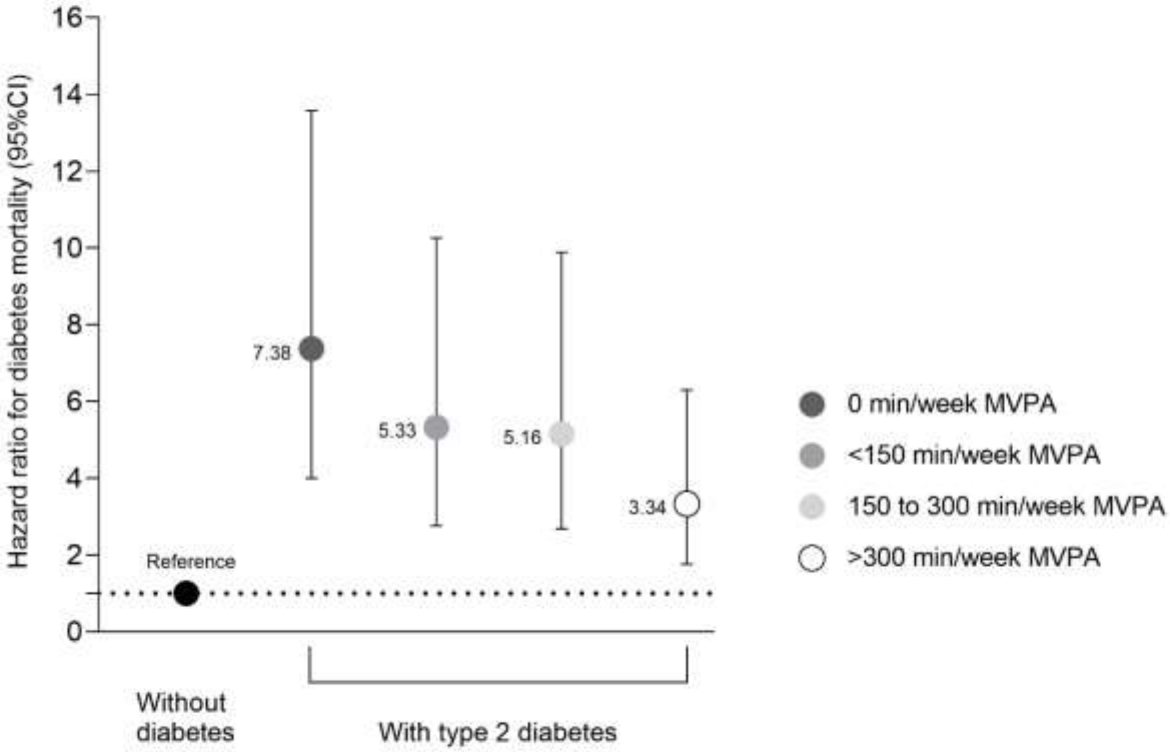

Table 1. Descriptive statistics for people with type 2 diabetes by moderate-to-vigorous physical activity level.

	All	**Moderate-to-vigorous physical activity (min/week)**			
		0	**0.1-149.9**	**150-300**	**>300**
	(n=41726)	(n=22159)	(n=8221)	(n=4759)	(n=6587)
Age, n(%)					
18-39 years	2603 (6.2)	1023 (4.6)	505 (6.1)	367 (7.7)	708 (10.8))
40-64 years	20090 (48.2)	9969 (45.0)	4206 (51.2)	2487 (52.3)	3428 (52.0)
65+ years	19033 (45.6)	11167(50.4)	3510 (42.7)	1905 (40.0)	2451 (37.2)
Sex, n(%)					
Men	18638 (44.7)	9033 (40.8)	3572 (43.4)	2290 (48.1)	3743 (56.8)
Women	23088 (55.3)	13126 (59.2)	4649 (56.6)	2469 (51.9)	2844 (43.2)
Ethnicity, n(%)					
White, non-Hispanic	23667 (56.7)	11950 (53.9)	4892 (59.5)	2857 (60.0)	3968 (60.3)
Black, non-Hispanic	8615 (20.7)	4959 (22.4)	1664 (20.2)	835 (17.6)	1157 (17.6)
Hispanic	7352 (17.6)	4330 (19.5)	1210 (14.7)	766 (16.1)	1046 (15.9)
Other	2089 (5.0)	918 (4.1)	455 (5.5)	301 (6.3)	415 (6.3)
Marital status, n(%)					
Married/living with partner	20120 (48.2)	9766 (44.1)	4113 (50.0)	2546 (53.5)	3695 (56.1)
Widowed/divorced/separated	17112 (41.0)	10102 (45.6)	3235 (36.4)	1685 (35.4)	2090 (31.7)
Never married	4408 (10.6)	2238 (10.1)	861 (10.5)	525 (11.0)	784 (11.9)
Educational level, n(%)					
Less than high school degree	12204 (29.3)	8254 (37.3)	1901 (23.1)	900 (18.9)	1149 (17.4)
High school degree or equivalent	12445 (29.8)	6926 (31.3)	2407 (29.3)	1336 (28.1)	1776 (27.0)
More than high school degree	16753 (40.2)	6745 (30.4)	3867 (47.0)	2503 (52.6)	3638 (55.2)
Smoking status, n(%)					
Never	20688 (49.6)	11079 (50.0)	4091 (49.8)	2406 (50.6)	3112 (47.2)
Former	14141 (33.9)	7140 (32.2)	2851 (34.7)	1686 (35.4)	2464 (37.4)
Current	6761 (16.2)	3840 (17.3)	1263 (15.4)	661 (16.9)	997 (15.1)
Alcohol consumption status, n(%)					
Never	9328 (29.3)	6104 (36.45)	1452 (23.0)	796 (21.2)	976 (19.1)
Former	9557 (30.0)	5339 (31.9)	1867 (29.6)	1046 (28.6)	1305 (25.6)
Current	12484 (39.2)	4998 (29.9)	2930 (46.4)	1783 (48.8)	2773 (54.4)
Body mass index, n(%)					
Non-overweight/obesity	6970 (16.7)	3815 (17.2)	1287 (15.7)	772 (16.2)	1096 (16.6)
Overweight	12915 (31.0)	6513 (29.4)	2421 (29.5)	1640 (34.5)	2341 (35.5)
Obesity	20382 (48.9)	10914 (49.3)	4267 (51.9)	2217 (46.6)	2984 (45.3)
Other medical conditions, n(%)					
None	8694 (20.8)	3953 (17.8)	1711 (20.8)	1204 (25.3)	1826 (27.7)
Hypertension	29509 (70.7)	16261 (73.4)	5880 (71.5)	3187 (67.0)	4181 (63.5)
Cancer	6208 (14.9)	3388 (15.3)	1243 (15.1)	676 (14.2)	901 (13.7)
Cardiovascular disease	14482 (34.7)	8780 (39.6)	2638 (32.1)	1339 (28.1)	1725 (26.2)
Activities of daily living limitations, n(%)	3108 (7.5)	2577 (11.6)	319 (3.9)	108 (2.3)	104 (1.6)
Diabetes medication, n(%)	35388 (84.8)	19198 (86.6)	6954 (84.6)	3948 (83.0)	5288 (80.3)
Diabetes duration, mean years (SD)	11.3 (12.0)	12.4 (12.9)	10.7 (11.1)	9.8 (10.7)	9.7 (10.6)

*Normal-weight: BMI <25 kg/m^2; Overweight: BMI 25-29.99 kg/m^2; Obesity: ≥30 kg/m^2

Table 2. Cause of death in people with type 2 diabetes and without diabetes at baseline.

	Without diabetes (n=459660)		Type 2 diabetes (n=41726)		
	Nº of deaths		Nº of deaths	HR (95% CI)	p
All-causes	48279	1 (ref)	11176	**1.26 (1.14 to 1.39)**	<0.001
Diabetes	533	1 (ref)	1153	**5.72 (3.15 to 10.39)**	<0.001
No-diabetes	47746	1 (ref)	10023	**1.21 (1.10 to 1.34)**	<0.001
CVD	10506	1 (ref)	2795	1.05 (0.87 to 1.28)	0.598
Kidney	754	1 (ref)	363	**2.55 (1.46 to 4.46)**	0.001
Cancer	12141	1 (ref)	2175	**1.47 (1.22 to 1.76)**	<0.001
Alzheimer	1262	1 (ref)	204	**2.08 (1.08 to 3.98)**	0.028
Other causes	23837	1 (ref)	4486	1.09 (0.93 to 1.28)	0.282

Analyses were adjusted for age, sex, ethnicity, marital status, educational level, smoking status, alcohol consumption, body mass index, hypertension, cancer, cardiovascular disease, limitations for activities of daily living, diabetes medication and diabetes duration. HR: Hazard ratio. CI: Confidence interval.

Table 3. Associations between moderate-to-vigorous physical activity categories and diabetes mortality in people with type 2 diabetes.

	Moderate-to-vigorous physical activity			
	0 min/week	<150 min/week	150 to 300 min/week	>300min/week
n/deaths	22159/803	8221/157	4759/104	6587/89
Model 1	1.00 (ref)	**0.66 (0.53 to 0.80)**	**0.64 (0.50 to 0.82)**	**0.38 (0.30 to 0.50)**
Model 2	1.00 (ref)	**0.62 (0.47 to 0.81)**	**0.58 (0.42 to 0.80)**	**0.37 (0.27 to 0.51)**
Model 3	1.00 (ref)	**0.64 (0.49 to 0.84)**	**0.61 (0.44 to 0.85)**	**0.40 (0.30 to 0.55)**
Model 4	1.00 (ref)	**0.68 (0.51 to 0.90)**	**0.66 (0.47 to 0.91)**	**0.43 (0.31 to 0.59)**
Model 5	1.00 (ref)	**0.71 (0.54 to 0.97)**	**0.68 (0.49 to 0.95)**	**0.44 (0.32 to 0.60)**

Results are hazard ratio (95% confidence interval).

Model 1: adjusted for age, sex, ethnicity, marital status and educational level.

Model 2: adjusted for model 1 + smoking status, alcohol consumption and body mass index.

Model 3: adjusted for model 2 + hypertension, cancer and cardiovascular disease.

Model 4: adjusted for model 3 + limitations for activities of daily living.

Model 5: adjusted for model 4 + diabetes medication and diabetes duration.

Values are HR (95% CI)