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Associations of objectively measured moderate-to-vigorous-intensity physical activity and sedentary time with all-cause mortality in a population of adults at high risk of type 2 diabetes mellitus

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ABSTRACT

The relationships of physical activity and sedentary time with all-cause mortality in those at high risk of type 2 diabetes mellitus (T2DM) are unexplored. To address this gap in knowledge, we examined the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time with all-cause mortality in a population of adults at high risk of T2DM. In 2010–2011, 712 adults (Leicestershire, U.K.), identified as being at high risk of T2DM, consented to be followed up for mortality. MVPA and sedentary time were assessed by accelerometer; those with valid data (≥10 hours of wear-time/day with ≥4 days of data) were included. Cox proportional hazards regression models, adjusted for potential confounders, were used to investigate the independent associations of MVPA and sedentary time with all-cause mortality. 683 participants (250 females (36.6%)) were included and during a mean follow-up period of 5.7 years, 26 deaths were registered. Every 10% increase in MVPA time/day was associated with a 5% lower risk of all-cause mortality [Hazard Ratio (HR): 0.95 (95% Confidence Interval (95% CI): 0.91, 0.98); p = 0.004]; indicating that for the average adult in this cohort undertaking approximately 27.5 minutes of MVPA/day, this benefit would be associated with only 2.75 additional minutes of MVPA/day. Conversely, sedentary time showed no association with all-cause mortality [HR (every 10-minute increase in sedentary time/day): 0.99 (95% CI: 0.95, 1.03); p = 0.589]. These data support the importance of MVPA in adults at high risk of T2DM. The association between sedentary time and mortality in this population needs further investigation.

1. Introduction

Diabetes is a leading health care burden nationally and internationally (NCD Risk Factor Collaboration, 2016). Therefore, the prevention of diabetes, particularly type 2 diabetes mellitus (T2DM), is an identified health care priority. Diabetes prevention has focused on the promotion of established health behaviours, including physical activity, with strong evidence of efficacy (Gillies et al., 2007). However, whilst the effects of promoting physical activity and other lifestyle factors on reducing the risk of T2DM are well-known in those at high risk of T2DM (defined as non-diabetic hyperglycaemia), the strength of association with all-cause mortality is less clear. To our knowledge, only one study has quantified the associations between objectively measured physical activity and mortality/morbidity outcomes in those at high risk of T2DM (Yates et al., 2014), whilst no studies have examined associations with objectively measured sedentary time. The latter is important given the mounting evidence that sedentary behaviour, defined as sitting or

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reclining with low energy expenditure, is associated with poor health and has been advocated as an important behavioural target in the prevention of diabetes (Henson et al., 2016).

This brief report quantifies the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time with all-cause mortality in a population of adults at high risk of T2DM recruited from primary care.

2. Methods

2.1. Design and population

Participants for this study were part of the Walking Away from Type 2 Diabetes trial (Yates et al., 2012). The trial consisted of adults at an increased risk of T2DM who were recruited in 2010–2011 through 10 primary care practices in Leicestershire, United Kingdom. Individuals (n = 833) with an increased risk of non-diabetic hyperglycaemia (defined as: impaired glucose tolerance (IGT) and/or impaired fasting glycaemia (IFG)) or undiagnosed T2DM were identified for recruitment using the Leicester Risk Score (Yates et al., 2012). At baseline, participants were randomised to usual care or the three-hour Walking Away structured education programme with ongoing annual support (Yates et al., 2012). Participants were followed up at 12, 24 and 36 months. Over the 36 months, no overall difference was observed in levels of physical activity or sedentary behaviour between the two arms (Yates et al., 2016). This brief report uses the baseline data and includes the 712 adults within the cohort who consented to have their records followed-up for health status. All participants provided written informed consent and the study was approved by the Nottingham Research Ethics Committee, United Kingdom.

2.2. Mortality data

Mortality data were obtained from the Office for National Statistics (ONS) via an application to the Health and Social Care Information Centre (HSCIC). All-cause mortality was defined as any death recorded between baseline and end of data linkage on 6 April 2016. All-cause mortality was coded as a binary variable representing censoring or death. For censored data, survival time (in days) was defined as the difference between the follow-up date (6 April 2016) and the date of baseline visit. For event data, survival time was defined as the difference between the date of death and baseline visit.

2.3. Physical activity and sedentary time data

MVPA and sedentary time were measured using an ActiGraph GT3X accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) which was worn on the right hip for seven consecutive days during waking hours. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, United Kingdom). The ActiGraph GT3X device was initialised to collect data using 15 seconds epochs, and files were reintegrated into one minute epochs. Accelerometer counts derived from the vertical axis were used to calculate the amount of time spent in sedentary behaviour (<100 cpm) and in MVPA (≥1952 cpm) (Freedson et al., 1998; Matthews et al., 2008). Non-wear time was defined as any periods of continuous zero counts for ≥60 consecutive minutes. Valid accelerometer data were defined as ≥10 hours of wear-time/day with ≥4 days of data. Participants who provided valid accelerometer data were retained for analysis. The average number of minutes/valid day spent sedentary and in MVPA were calculated.

2.4. Anthropometric, demographic and lifestyle data

The following data were also utilised: age (years), body mass index (BMI: kg/m^2), ethnicity (white, non-white), sex (male, female), smoking status (non-smoker, smoker), medical history of cardiovascular disease (myocardial infarction, heart failure, angina and/or stroke), blood pressure and/or cholesterol medication (ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, beta-blockers, calcium channel blockers, lipid lowering statins and/or lipid lowering fibrates), aspirin medication, and accelerometer wear-time. Body weight (Tanita TBE 611; Tanita, West Drayton, United Kingdom) and height were measured to the nearest 0.1 kg and 0.5 cm, respectively. BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres).

2.5. Statistical analysis

Statistical analyses were conducted using Stata/MP V14.0 (Stata Corporation, College Station, Texas, USA). Data were analysed in August 2016.

Participant characteristics, stratified by mortality status, were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations. A series of Cox proportional hazards regression models (with survival time in days) were used to investigate the independent associations of MVPA and sedentary time with all-cause mortality (Cox, 1972). MVPA time indicated a non-normal distribution; therefore, it was log-transformed to reduce the influence of skewed data. To ensure that the hazard ratios represented a 10% increase in MVPA time/day, a log base of 1.1 (i.e. $\log_{1.1}$ (MVPA time)) was used. Sedentary behaviour was presented as a 10-minute increase in sedentary time/day. Model 1 adjusted for: age, sex and smoking status. Model 2 further adjusted for sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis). Model 3 further adjusted for BMI. Ethnicity, accelerometer wear-time, medical history of cardiovascular disease, blood pressure and/or cholesterol medication, and aspirin medication were also individually considered as covariates in the minimally adjusted model (i.e. Model 1). However, their inclusion did not affect the hazard ratios, direction of association or interpretation (significance/non-significance) of the models (see Supplementary Table S1). Therefore, in order to maintain an adequate ratio between the number of events and covariates in the model (Vittinghoff and McCulloch, 2007), the more parsimonious model was used.

The proportional hazards assumption of each model was assessed via: a) plotting the Schoenfeld residuals against time; and b) executing a formal post-hoc proportional hazards global test (Stata command: 'estat phtest'). All reported p-values were two-sided with $p < 0.05$ considered statistically significant.

2.6. Sensitivity analysis

Since smokers are generally more likely to be physically inactive in comparison to non-smokers, they could potentially modify the associations with all-cause mortality. Therefore, in order to assess the robustness and replicability of our findings, we repeated our main analysis (Models 1, 2 and 3) in the sample of non-smokers.

3. Results

Of the 712 individuals who consented for data linkage, 683 participants [mean age (standard deviation (SD)) = 63.6 (7.8) years; mean BMI (SD) = 32.0 (5.3) kg/m^2; 250 females (36.6%)] provided valid accelerometer data and were included for analysis. During a mean follow-up period of 5.7 years, 26 deaths were registered. Table 1 displays the characteristics of the included participants further stratified by mortality status.

In the maximally adjusted model (Model 3), every 10% increase in MVPA time/day was associated with a 5% lower risk of all-cause mortality [Hazard Ratio (HR): 0.95 (95% Confidence Interval (95% CI): 0.91, 0.98); p = 0.004]. Conversely, sedentary time showed no association with all-cause mortality [HR (every 10-minute increase in sedentary time/day): 0.99 (95% CI: 0.95, 1.03); p = 0.589]. The proportional

Table 1
Participant characteristics stratified by mortality status (Walking Away from Type 2 Diabetes trial, 2010–2011, Leicestershire, United Kingdom).

Characteristic	Sample (n = 683)	Censored (n = 657)	Deaths (n = 26)
Age (years)[a]	63.6 (7.8)	63.6 (7.8)	64.4 (8.0)
Body mass index (kg/m^2)[a]	32.0 (5.3)	32.0 (5.3)	33.2 (6.8)
Ethnicity[b]			
White	608 (89.0)	584 (88.9)	24 (92.3)
Non-white	75 (11.0)	73 (11.1)	2 (7.7)
Sex[b]			
Male	433 (63.4)	412 (62.7)	21 (80.8)
Female	250 (36.6)	245 (37.3)	5 (19.2)
Smoking status[b]			
Non-smoker	630 (92.2)	609 (92.7)	21 (80.8)
Smoker	53 (7.8)	48 (7.3)	5 (19.2)
Medical history of cardiovascular disease[b]			
No	609 (87.2)	589 (89.7)	20 (76.9)
Yes	74 (10.8)	68 (10.3)	6 (23.1)
Currently taking blood pressure and/or cholesterol medication[b]			
No	295 (43.2)	285 (43.4)	10 (38.5)
Yes	388 (56.8)	372 (56.6)	16 (61.5)
Currently taking aspirin medication[b]			
No	577 (84.5)	559 (85.1)	18 (69.2)
Yes	106 (15.5)	98 (14.9)	8 (30.8)
Accelerometer wear-time (average number of minutes per valid day)[a]	855.5 (79.2)	856.3 (79.0)	834.6 (81.7)
Moderate-to-vigorous-intensity physical activity time (average number of minutes per valid day)[a]	27.5 (24.4)	27.8 (24.5)	19.0 (19.5)
Sedentary time (average number of minutes per valid day)[a]	538.0 (92.1)	537.5 (91.1)	551.5 (116.5)
Survival time (number of years)[a]	5.6 (0.5)	5.7 (0.2)	3.9 (1.4)

[a] Continuous variable: mean (standard deviation).
[b] Categorical variable: number (%).

hazards assumption of each model was satisfied with the Schoenfeld residuals showing no trend with time and all global tests reporting $p > 0.05$. Table 2 displays the results from the Cox proportional hazards regression analyses.

Supplementary Table S1 displays the findings of the minimally adjusted model (Model 1) that individually considered all other confounders.

Supplementary Table S2 displays the findings of the sensitivity analysis where the main analysis (Models 1, 2 and 3) was repeated in the sample of non-smokers (n = 630; mean follow-up period of 5.6 years; 21 deaths). Our findings were robust and generalizable.

4. Discussion

Our findings demonstrate that the risk of death was reduced by 5% for every 10% increase in MVPA time in adults at high risk of T2DM. This indicates that for the average adult in this cohort undertaking approximately 27.5 minutes of MVPA/day, this benefit would be associated with only 2.75 additional minutes of MVPA/day. In contrast, sedentary time was not associated with all-cause mortality.

Previous research has consistently shown that both MVPA and sedentary behaviour are associated with all-cause mortality (Biswas et al., 2015; Nocon et al., 2008; Samitz et al., 2011; Wilmot et al., 2012). However, the majority of the studies in this research area have been limited by self-reported measures, which rely on recall and suffer from response bias; hence, they tend to have low validity and high levels of measurement error. Few studies have examined the associations of MVPA and sedentary time with mortality using objective measurements. In a national sample of US adults with objectively measured data, Schmid and colleagues observed that both low levels of MVPA and high levels of sedentary behaviour were independently associated with early all-cause mortality (Schmid et al., 2015). Other studies have reported similar findings (Fishman et al., 2016; Loprinzi et al., 2016). In contrast, a recent study in a subset of participants with diabetes from this national survey showed no associations between sedentary time and all-cause mortality after adjusting for total physical activity (Loprinzi and Sng, 2016). However, all of these studies utilised the same survey dataset; thus, the relationships need testing in other populations including those at a high risk of T2DM.

Our results for MVPA are consistent with other studies that have looked at the associations of pedometer assessed physical activity or cardiorespiratory fitness with mortality in similar cohorts. An international study reported that the risk of cardiovascular disease morbidity and mortality was reduced by 8% for every 2000 steps/day increase in walking activity (corresponds to approximately 20 minutes/day of MVPA based on a cadence of 100 steps/minute) in those at high risk of T2DM (Yates et al., 2014), with another study showing that the risk of mortality was reduced with higher fitness in those with IGT or undiagnosed T2DM (Lyerly et al., 2009).

4.1. Strengths and limitations

This study has strengths and limitations. Strengths include the utilisation of objectively measured MVPA and sedentary behaviour data; a high risk sample; and a robust statistical analysis plan. The key limitation was the low number of events. However, it has previously been shown that Cox proportional hazards regression analysis can potentially be considered as a robust estimation method even with a low number of events. A ratio of the number of events to the number of predictor variables of approximately 5 or more has been shown to produce accurate estimates in Cox proportional hazards models (Vittinghoff and McCulloch, 2007). In our study, the principles of parsimony were followed and only a small number of key covariates were adjusted for; this also prevented any overfitting of the models. However, although our findings were unaffected after additionally adjusting for other potential confounders (ethnicity, accelerometer wear-time, medical history of cardiovascular disease, blood pressure and/or cholesterol medication, and aspirin medication) it is possible that other factors

Table 2
Cox proportional hazards regression models showing the associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time with all-cause mortality (Walking Away from Type 2 Diabetes trial, 2010–2011, Leicestershire, United Kingdom).

Cox proportional hazards regression model	$\log_{1.1}$ (MVPA time (minutes/day))		Sedentary time (10 minutes/day)	
	Hazard ratio (95% CI)[a]	p-Value	Hazard ratio (95% CI)[b]	p-Value
Model 1	**0.94 (0.91, 0.98)**	**0.001**	1.01 (0.97, 1.06)	0.538
Model 2	**0.94 (0.91, 0.97)**	**0.001**	0.99 (0.95, 1.03)	0.604
Model 3	**0.95 (0.91, 0.98)**	**0.004**	0.99 (0.95, 1.03)	0.589

Bold indicates statistical significance at p-value = 0.05.
Model 1 adjusted for: age, sex and smoking status.
Model 2 further adjusted for: sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis).
Model 3 further adjusted for: body mass index.
[a] Hazard ratios represent the risk of all-cause mortality for every $\log_{1.1}$-unit increase in MVPA time/day (i.e. for every 10% increase in MVPA time/day).
[b] Hazard ratios represent the risk of all-cause mortality for every 10-unit increase in sedentary time/day (i.e. for every 10-minute increase in sedentary time/day).

were confounding the associations or that reverse causation was contributing to the observed association between MVPA and all-cause mortality. In addition to the ratio of events per predictor variable, large regression coefficients and high correlations between predictor variables can cause issues in the approximation process (Courvoisier et al., 2011). All of our model coefficients were small and there were low correlations between the predictors in our models (data not shown). Nevertheless, these results should be interpreted with caution; in particular, the non-significant association with sedentary time could be due to a type II error arising from a lack of statistical power.

5. Conclusions

In conclusion, these data support the importance of MVPA in adults at high risk of T2DM. However, more research is required to assess whether objectively measured sedentary time is associated with health outcomes in those at high risk of T2DM independently of MVPA.

Ethical approval

The Walking Away from Type 2 Diabetes trial was approved by the Nottingham Research Ethics Committee, United Kingdom.

Conflicts of interest

None.

Contribution statement

TY had the original idea for the analysis, which was further developed and refined by all authors. TY and KB had access to the mortality data. CE processed the accelerometer data. KB carried out the statistical analysis and wrote the first draft of the manuscript. All authors edited and reviewed the manuscript and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pmedr.2017.01.013.

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