Physical Activity and Risk of All-Cause and Cardiovascular Disease Mortality in Diabetic Adults From Great Britain: Pooled Analysis of 10 Population-Based Cohorts

Kabir P. Sadarangani,[1,4] Mark Hamer,[1,2] Jenny S. Mindell,[1] Ngaire A. Coombs,[1,2] and Emmanuel Stamatakis[1,2,3]

OBJECTIVE

To examine associations between specific types of physical activity and all-cause and cardiovascular disease (CVD) mortality in a large nationally representative sample of adults with diabetes from Great Britain.

RESEARCH DESIGN AND METHODS

There were a total of 3,038 participants (675 deaths) with diabetes in the Health Survey for England and the Scottish Health Surveys conducted between 1997 and 2008. Participants aged ≥50 years at baseline were followed up for an average of 75.2 months for all-cause and CVD mortality. Data were collected on self-reported frequency, duration, and intensity of participation in sports and exercise, walking, and domestic physical activity, from which the number of MET-hours/week were derived. Sex-specific medians of time spent in each type of physical activity (for those physically active) were calculated, and Cox proportional hazards regression conducted to examine type-specific associations between the level of physical activity and all-cause and CVD mortality risk.

RESULTS

Inverse associations with all-cause and CVD mortality were observed for overall physical activity in a dose-response manner after adjusting for covariates. Compared with those who individuals were inactive, participants who reported some activity, but below the recommended amount, or who met the physical activity recommendations had a 26% (95% CI 39–11) and 35% (95% CI 47–21) lower all-cause mortality, respectively. Similar results were found for below/above median physical activity levels. Sports and exercise participation was inversely associated with all-cause (but not CVD) mortality, as were above average levels of walking. Domestic physical activity was not associated with mortality.

CONCLUSIONS

Moderate physical activity levels were associated with better prognosis in diabetic adults.

[1]Department of Epidemiology and Public Health, University College London, London, U.K.
[2]Physical Activity Research Group, Division of Population Health, University College London, London, U.K.
[3]Prevention Research Collaboration, Sydney School of Public Health, University of Sydney, Sydney, New South Wales, Australia
[4]Escuela de Kinesiología, Facultad de Medicina, Universidad Diego Portales, Santiago, Chile

Corresponding author: Kabir P. Sadarangani, kabir.sadarangani@gmail.com.

Diabetes is a major cause of illness and premature death in most countries, causing 4.6 million deaths in 2011 (1). The incidence and prevalence of diabetes, and associated burden of disease, are continuing to increase in most countries of the world (1). In the U.K., diabetes was diagnosed in 3.1 million people in 2011 (1), with estimates for undiagnosed diabetes increasing this figure by up to half a million individuals (2). The prevalence of diabetes among adults in Scotland almost doubled between 2003 and 2008, from 5.2 to 9.6% (3), and it has been forecast that by 2025 there will >4 million people in the U.K. who have received a diagnosis of diabetes (4). This increasing prevalence of diabetes is alarming, as diabetes is a strong risk factor for coronary heart disease and cardiovascular disease (CVD) mortality (5).

Conventional efforts to reduce the impact of diabetes complications have been predominantly aimed at controlling hyperglycemia, hypertension, and dyslipidemia by medication. However, diabetes management recommendations extend to an overall strategy including lifestyle modification to reduce the risk of complications (6).

Prospective cohort studies have shown that diabetic patients who engage in regular physical activity have a lower risk of CVD and all-cause mortality than those who are less active (7–15). Randomized controlled trials of structured exercise training among diabetic patients have shown the beneficial effects on insulin sensitivity, glycemic control, and weight loss or maintenance (16–21), although behavioral interventions designed to deliver physical activity advice did not demonstrate a significant benefit compared with usual care (21). Thus, although supervised exercise appears to be effective in managing diabetes, patients struggle to maintain sufficient physical activity in their daily life outside a controlled trial setting. It is therefore important to investigate the role of lifestyle activity for secondary prevention in diabetic patients. The 2011 physical activity report by the Chief Medical Officers of the U.K. (22) recommends that adults with diabetes should engage in aerobic physical activity of moderate intensity for at least 150 min/week (e.g., 5 days a week for 30 min), 75 min of vigorous activity, or an equivalent combination, a recommendation that is identical to the one aimed at adults in the general population. We are not aware of any epidemiological studies that have investigated the role of different types of physical activity on prognosis in diabetic patients. Thus, the key aim of this study was to examine the association between not only total physical activity but also different physical activity types and the risk of all-cause and CVD mortality in a population sample of diabetic patients drawn from representative general population samples from England (Health Survey for England [HSfE]) and Scotland (Scottish Health Survey [SHeS]).

RESEARCH DESIGN AND METHODS

Study Design and Population

The HSfE and the SHeS are cross-sectional, general, representative population-based surveys among individuals living in private households in the two countries. The samples are selected from a multistage, stratified probability design to give a sociodemographic nationally representative target population (23). The HSfE has been conducted annually since 1991 (24), whereas the SHeS was initially run as intermittent surveys in 1995, 1998, and 2003 (25,26); both were designed as health examination surveys to measure health and health-related behaviors. Trained interviewers visited the selected households to recruit participants and elicit answers to questionnaires. A trained nurse then visited consenting households to obtain information on medication, measure blood pressure, and collect blood samples (24,26). Each HSfE and the SHeS was approved by the relevant research ethics committees in England and Scotland. From 1993 onward, participants aged ≥16 years were asked for written consent to have their names flagged on the National Health Service Central Register (for mortality). This study includes individuals aged ≥50 years of age with type 1 or 2 diabetes at baseline from the HSfE of 1997, 1998, 1999, 2003, 2004, 2006, and 2008, and the SHeS of 1995, 1998, and 2003, with the corresponding linkage to mortality data. Diabetes status was defined using the following multiple criteria: self-reported physician-diagnosed diabetes in response to a direct question; reporting diabetes as a long-standing illness; and a baseline glycated hemoglobin A_{1c} (HbA$_{1c}$) level of ≥6.5% (48 mmol/mol) (27).

Using these criteria, we identified 4,456 individuals aged ≥50 years with diabetes. After excluding participants without information on vital status at follow-up (lack of consent or inability to link data, n = 705), physical activity (n = 1), or other covariates (smoking status, drinking pattern, measured BMI, social class, limiting long-standing illness, and preexisting CVD and hypertension, n = 712), the final analytical sample included 3,038 individuals. Inclusion of the younger age groups of patients with diabetes (35–49 years of age, n = 617) would have considerably diluted the overall event rate as there were only 28 all-cause deaths and only 12 CVD deaths in this age group. Such dilution of the events rate would have adversely impacted the precision of our effect size estimates.

Physical Activity Assessment

The interviewer inquired about participation in physical activities for the 4 weeks prior to the HSfE/SHeS interview (24). Overall participation, type of activity, and frequency (occasions) of participation were examined for the following three physical activity domains: domestic physical activity, walking, and sports and exercise.

For domestic physical activity, individuals were asked about their participation (yes/no) in heavy manual housework, gardening, and "do-it-yourself" activities that lasted ≥30 min (4 weeks prior to the interview). All heavy domestic physical activity was defined as moderate intensity (28). Walking intensity was assessed by asking participants to rate their pace (slow/average/fairly brisk/fast) with the latter two responses categorized as moderate intensity. For sports and exercise, participants were asked for the frequency, duration, and name of the

sport/exercise that lasted ≥15 min (e.g., cycling, swimming, aerobics, football, and rugby). Intensity was also assessed by asking the individual if the particular sport/exercise made them feel "out of breath or sweaty." The physical activity questionnaires had minor differences across survey years. The minimum duration for a walking bout to be included in the analysis was 15 min in 1997 and 1998, but 30 min in 2003. To ensure compatibility between the long (1997, 1998) and short (2003) versions of the questionnaire, all activity sessions that lasted <30 min in 1997 and 1998 were excluded.

Mortality Outcome

Primary causes of death were diagnosed according to the ICD using ICD-9 and ICD-10. CVD codes recorded from the ICD were 390–459 from the ICD-9 and 101–199 from the ICD-10 (28).

Covariates

Height and weight were measured by trained interviewers using standard protocols (29); BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Hypertensive status was defined using the following multiple criteria: self-reported doctor-diagnosed hypertension, hypertension reported as a long-standing illness, and blood pressure recordings measured by the nurse (hypertension: mean of second and third readings for systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg) (30). Additional questions assessed social class, alcohol consumption, smoking habits, existing CVD, and existing limiting long-standing illness.

Data Handling and Analysis

All analyses were performed using Stata 11 (StataCorp, LP). Specific physical activity types were recoded into MET intensity levels. A MET is defined as the ratio of work metabolic rate during a specific physical activity to a reference rate of metabolic rate at rest of 1.0 (31). The conversion to MET-hours/week for walking, sports/exercise, and domestic physical activity has been described in detail elsewhere (32) using the Compendium of Physical Activity (31). MET-hours were calculated by multiplying the MET value of a given activity by the total weekly volume in hours. Physical activity variables

included in this study as main exposures were as follows: 1) total nonoccupational physical activity; 2) sports/exercise; 3) domestic physical activity; 4) walking; and 5) physical activity grouped in relation to the current recommendation guidelines (all expressed as MET-hours/week).

The physical activity recommendation variable was created based on participation in moderate to vigorous leisure-time physical activities. This variable was based on the intensity with which an individual participated in physical activity multiplied by the duration per day (hours/week) in each activity type. The recommended cut point of 7.5 MET-hours/week was used. It was calculated from the product of 2.5 h and 3 MET-hours, corresponding to the physical activity recommendations (150 min/week of moderate-intensity exercise) (33). Participants were classified into the following three groups: no (nonoccupational) physical activity (0 MET-hours/week; reference value); some physical activity but lower than the recommended activity (0.1–7.4 MET-hours/week); and meeting the physical activity recommendations (≥7.5 MET-hours/week). Sex-specific median MET values for total nonoccupational physical activity, sports/exercise, domestic activity, and walking were also calculated (Supplementary Table 1).

Hazard ratios (HRs) and 95% CIs of all-cause and CVD mortality (outcomes) were calculated using Cox proportional hazards regression (with months as the time scale). Data were censored on 15 February 2011 for the HSfE and on 30 December 2009 for the SHeS for those individuals who did not have an event. The proportional hazards assumption was tested visually using Kaplan-Meier curves, and no apparent violations were observed. Within each analysis (physical activity in relation to the current recommendation guidelines), the following adjustments were performed: initially for age and sex (model 1); additionally, for social class (I, professional; II, managerial technical; IIIN, skilled nonmanual; IIIM, skilled manual; IV, semiskilled manual; V, unskilled manual; and other, including students/never worked/armed forces);

for alcohol consumption (never drinkers; ex-drinkers; less than one drink per month; one to two drinks per month; one to four drinks per week; and five or more drinks per week); for smoking (never smoked; ex-smoker; <10 cigarettes per day; 10–19 cigarettes per day; and ≥20 cigarettes per day); BMI; physical activity questionnaire version; hypertension (yes/no); limiting long-standing illness (yes/no); and existing CVD (yes/no) (model 2).

Moreover, within each analysis (for different types of physical activity) the following adjustments were performed, initially for age and sex (model 1), additionally for hypertension, limiting long-standing illness, social class, alcohol consumption, smoking, BMI, physical activity questionnaire version, existing CVD (model 2), and for other physical activity types (model 3). Test for linear trend was obtained using the continuous measure of MET-minutes of activity in place of the categorical variables.

Likelihood ratio tests were performed to assess for interactions among sex, BMI, existing CVD, and physical activity in terms of all-cause and CVD mortality.

RESULTS

Table 1 summarizes the sample characteristics by level of physical activity. A total of 40% of the participants met the physical activity recommendation guidelines, but 33% reported no physical activity. Individuals not reporting any physical activity were older, more likely to be from a lower socioeconomic group, more likely to have a limiting long-standing illness other than diabetes, and to have CVD at baseline compared with those doing some physical activity ($P < 0.001$). Participants who met physical activity recommendation guidelines were more likely to be male and nonsmokers, and to have a lower BMI than those who performed some or no physical activity ($P < 0.004$).

Associations Between Summary Physical Activity Levels and Mortality

Table 2 illustrates the associations between physical activity and all-cause and CVD mortality.

Table 1—Descriptive characteristics of the sample at baseline by summary physical activity category among patients with diabetes aged 50 and over

| | Physical activity group* | | | |
Variables	None (N = 1,002)	Some (N = 818)	Meets recommendations (N = 1,218)	P value
Categorical variables				
Male sex	51	51.8	58.7	<0.001
Social class of HOH/HRP (semiskilled manual and lower)	66	56.1	50.2	<0.001
Smoking status (nonsmokers)	42.6	40.2	43.8	0.003
Alcohol status (nondrinkers)	21.1	12.1	11.7	<0.001
With a long-standing illness (other than diabetes)	76.3	58.3	40.4	<0.001
With hypertension†	56.1	49.1	50.2	0.004
With existing CVD‡	18.6	13.9	7.6	<0.001
Continuous variables				
Age (years)	68.1 (9.4)	67.1 (9.3)	64.5 (8.2)	<0.001
BMI (kg/m^2)	30.2 (5.5)	30.3 (5.3)	29.5 (4.8)	<0.001

Data are % or mean (SD), unless otherwise stated. HoH/HRP, head of household/household reference person. *Nonoccupational physical activity: none <0.1, some 0.1–7.4, and meets recommendations ≥7.5 MET-hours/week. †Hypertension was defined as follows: doctor-diagnosed hypertension; systolic/diastolic blood pressure ≥140/90 mmHg, respectively; or long-standing illness or hypertension. ‡Long-standing illness or doctor-diagnosed CVD (stroke, angina, heart attack).

In total, 675 people died (22.2%), 270 (8.9%) from CVD, with a median follow-up time of 75.2 months, and mortality rates of 2.8 and 1.1 per 1,000 person-months for all-cause and CVD, respectively.

Higher physical activity was associated with lower mortality. Compared with those individuals not undertaking physical activity, the greatest reduction in the risks of both all-cause mortality (HR 0.62 [95% CI 0.51–0.74]) and CVD mortality (0.57 [0.42–0.76]) were observed in those meeting the physical activity recommendations; these associations persisted after adjustment for all covariates. Reduced risk of both all-cause and CVD mortality was also observed in the group who reported performing some physical activity, after adjustment for covariates.

A sensitivity analysis was conducted (the results of which are presented in Supplementary Tables 1 and 3) separately for the 393 participants (180 women, 213 men) with undiagnosed diabetes (whose inclusion in our sample was based on HbA$_{1c}$ levels) and for the 2,645 participants (1,208 women, 1,437 men) with diagnosed diabetes (whose inclusion in our sample was based on doctor-diagnosed and/or long-standing illness).

Among participants with diagnosed diabetes (n = 2,645; Supplementary Table 2), a total of 629 people died from any cause, and 252 from CVD causes, with a median follow-up time of 75.4 months, and mortality rates of 3.0 and 1.2 per 1,000 person-months, respectively.

The direction and magnitude of the observed associations were very similar

to those in the main analyses (Table 2); for example, the multivariable-adjusted HR for those meeting the physical activity recommendations was 0.64 (95% CI 0.52–0.80; P < 0.001) for all-cause mortality and 0.60 (0.43–0.84; P < 0.001) for CVD mortality, compared with those undertaking no physical activity.

We found no evidence for sex, BMI, or existing CVD interactions with either of our two mortality outcomes.

Among participants with undiagnosed diabetes (n = 393; Supplementary Table 3), a total of 46 people died from any cause (11.70%), and 18 people died from CVD causes (4.58%), with a median follow-up time of 75.4 months, and mortality rates of 1.48 and 0.58 per 1,000 person-months, respectively.

The very low number of events in this subgroup and the subsequent violations of the proportional hazards assumptions limit the value of this subanalysis (e.g., there were only nine all-cause deaths and only three CVD deaths in the middle physical activity group). Although no statistically significant associations were observed, there were indications that the HRs were following a dose-response pattern in both the all-cause and CVD mortality analyses. Because of the limited statistical power, we preferred to place these data in Supplementary Table 3.

Tables 3 and 4 show the associations between different types of physical activity and all-cause and CVD mortality, respectively. There was a dose-response relationship between higher levels of overall physical activity and lower risk of all-cause and CVD mortality, as follows: compared with those who were inactive, the age- and sex-adjusted HR for all-cause mortality was 0.80 (95% CI

Table 2—Cox regression models for the association of baseline physical activity with all-cause and CVD mortality in patients with diabetes aged 50 and over

Variables	Events	Model 1*	Model 2†
Physical activity level‡			
None (reference)	297/125	1.00/1.00	1.00/1.00
Some, below recommended	184/71	0.80 (0.67–0.96)/0.74 (0.55–0.99)	0.74 (0.61–0.89)/0.68 (0.51–0.92)
Recommended or above	194/74	0.62 (0.51–0.74)/0.57 (0.42–0.76)	0.65 (0.53–0.79)/0.60 (0.44–0.82)
P trend		<0.001	<0.001

Data are given as all cause/CVD and HR (95% CI). *Adjusted for age and sex. †Additional adjustments for hypertension, limiting long-standing illness, social class, alcohol consumption, smoking, BMI, physical activity questionnaire version, and existing CVD. ‡Nonoccupational physical activity: none <0.1, some 0.1–7.4, and meets recommendations ≥7.5 MET-hours/week.

Table 3—Associations between specific activity types and all-cause mortality in an older population sample of patients with diabetes

Variables	N	Events	Model 1*	Model 2†	Model 3‡
Total MET-hours/week§					
None (reference)	1,002	297	1.00	1.00	—
Below median	1,017	224	0.8 (0.67–0.95)	0.74 (0.62–0.89)	—
Above median	1,019	154	0.59 (0.48–0.72)	0.62 (0.50–0.77)	—
P trend			<0.001	<0.001	
Sports and exercise MET-hours/week‖					
None (reference)	2,374	586	1.00	1.00	1.00
Below median	346	51	0.68 (0.51–091)	0.72 (0.54–0.97)	0.74 (0.55–0.99)
Above median	318	38	0.62 (0.44–0.86)	0.68 (0.49–0.95)	0.71 (0.51–0.99)
P trend			<0.001	0.005	0.011
Walking MET-hours/week¶					
None (reference)	1,464	380	1.00	1.00	1.00
Below median	789	176	0.91 (0.76–1.09)	0.87 (0.72–1.05)	0.91 (0.75–1.10)
Above median	785	119	0.62 (0.51–0.77)	0.66 (0.53–0.82)	0.68 (0.54–0.85)
P trend			<0.001	<0.001	0.001
Domestic MET-hours/week#					
None (reference)	1,879	468	1.00	1.00	1.00
Median	579	97	0.75 (0.60–0.93)	0.73 (0.59–0.91)	0.77 (0.61–0.97)
Above median	580	110	0.94 (0.76–1.17)	0.99 (0.79–1.23)	1.08 (0.86–1.36)
P trend			0.195	0.337	0.943

Data are HR (95% CI), unless otherwise stated. *Adjusted for age and sex. †Also adjusted for hypertension, limiting long-standing illness, social class, alcohol consumption, smoking, BMI, physical activity questionnaire version, and existing CVD. ‡Also mutually adjusted for other physical activity types. §Total MET-hours/week nonoccupational physical activity: median 12.4 for male participants, 9.4 for female participants. ‖Total MET-hours/week of sports and exercise: median 8.0 for male participants, 5.8 for female participants. ¶Total MET-hours/week of walking: median 5.4 for male participants, 4.7 for female participants. #Total MET-hours/week of domestic physical activity: median 7.1 for male participants, 5.2 for female participants.

0.67–0.95) among those who reported below average physical activity, and 0.59 (0.48–0.72) among those reporting above average physical activity levels. The same trend was observed after multivariate adjustment (model 2).

Participation in sports/exercise was also associated with a lower risk of all-cause mortality in a dose-response manner; however, associations were attenuated after adjusting for covariates and other activity types (models 2 and 3). Conversely (for CVD mortality), compared with participants who reported no sports/exercise, the age- and sex-adjusted HR for those reporting below average sports/exercise was 0.57 (95% CI 0.35–0.93); but after adjusting for additional covariates (model 2) and other physical activity types (model 3), this association was attenuated to the null.

Walking was associated with a lower risk of both all-cause and CVD mortality, but adjusting the corresponding CVD models for other physical activity types attenuated these associations (model 3, P for trend = 0.055). Since we found evidence for sex interactions between walking and all-cause mortality

($P = 0.037$), we stratified the corresponding analyses by sex (Supplementary Table 4). These stratified analyses revealed a consistent dose-response pattern in men but not in women, in whom only the above median walking group had a lower risk of all-cause mortality compared with the referent group. However, male participants had a higher median level of walking than female participants (5.4 MET-hours/ week for men compared with 4.7 MET-hours/week for women), so the differential dose-response by sex may be due to lower BMI ($P < 0.001$), lower prevalence of limiting long-standing illness ($P = 0.008$) and hypertension ($P = 0.004$), and the use of a higher cutoff to signify "high" amounts of walking for male compared with female participants.

We found no consistent evidence for an association between domestic physical activity and all-cause or CVD mortality in any model.

CONCLUSIONS

This study provides evidence of a dose-response relationship between physical

activity and all-cause and CVD mortality among diabetic adults. These findings are in agreement with other prospective studies (9–13) showing a protective effect for all-cause and CVD mortality. For example, compared with diabetic individuals who have low activity levels, Hu et al. (12) found that those classified as medium and high for physical activity had HRs of 0.61 (95% CI 0.53–0.70) and 0.52 (0.45–0.60) for total mortality, and 0.61 (0.52–0.73) and 0.52 (0.44–0.62) for CVD mortality, respectively. Moreover, another study by the same group (11) found that patients with diabetes engaging in two or three types of moderate to high levels of occupational, commuting, and leisure-time physical activity (highest participation group) had a 45–48% and a 44–48% reduction in all-cause and CVD mortality, respectively, compared with those who reported light levels of physical activity. However, comparison with prior studies is problematic because the measurement scales and definitions of physical activity used differ.

We also presented evidence that even relatively low amounts of physical

Table 4—Associations between specific activity types and CVD mortality in an older population sample of patients with diabetes

Variables	N	Events	Model 1*	Model 2†	Model 3‡
Total MET-hours/week§					
None (reference)	1,002	125	1.00	1.00	—
Below median	1,017	83	0.71 (0.54–0.94)	0.66 (0.50–0.88)	—
Above median	1,019	62	0.57 (0.42–0.78)	0.62 (0.44–0.86)	—
P trend			<0.001	0.002	
Sports and exercise MET-hours/week‖					
None (reference)	2,374	236	1.00	1.00	1.00
Below median	346	17	0.57 (0.35–093)	0.64 (0.38–1.05)	0.65 (0.39–1.08)
Above median	318	17	0.69 (0.42–1.13)	0.76 (0.46–1.27)	0.79 (0.48–1.32)
P trend			0.026	0.105	0.149
Walking MET-hours/week¶					
None (reference)	1,464	153	1.00	1.00	1.00
Below median	789	68	0.88 (0.66–1.18)	0.86 (0.64–1.15)	0.89 (0.66–1.21)
Above median	785	49	0.65 (0.47–0.89)	0.69 (0.49–0.97)	0.71 (0.50–1.00)
P trend			0.009	0.032	0.055
Domestic MET-hours/week#					
None (reference)	1,879	188	1.00	1.00	1.00
Below median	579	41	0.79 (0.56–1.11)	0.78 (0.55–1.10)	0.82 (0.58–1.16)
Above median	580	41	0.89 (0.63–1.25)	0.96 (0.67–1.37)	1.05 (0.72–1.51)
P trend			0.304	0.499	0.887

Data are HR (95% CI), unless otherwise stated. *Adjusted for age and sex. †Also adjusted for hypertension, limiting long-standing illness, social class, alcohol consumption, smoking, BMI, physical activity questionnaire version, and existing CVD. ‡Also mutually adjusted for other physical activity types. §Total MET-hours/week nonoccupational physical activity: median 12.4 for male participants, 9.4 for female participants. ‖Total MET-hours/week of sports and exercise: median 8.0 for male participants, 5.8 for female participants. ¶Total MET-hours/week of walking: median 5.4 for male participants, 4.7 for female participants. #Total MET-hours/week of domestic physical activity: median 7.1 for male participants, 5.2 for female participants.

activity are associated with reduced risk of all-cause and CVD mortality. These findings are consistent with the study conducted by Sluik et al. (15), which found that diabetic individuals classified as moderately active (third quartile) for total physical activity exposure, showed a 38% reduction (95% CI 0.49–0.78) in all-cause mortality and a 49% reduction (0.32–0.81) in CVD mortality, compared with those classified as inactive in multivariable analysis (15).

Evidence from our study of a dose-response relationship between sports/exercise and all-cause mortality are in agreement with that of other previous studies (7,8,11,14,15). For example, our study found that patients with diabetes reporting high levels of physical activity had all-cause mortality levels of 29% (95% CI 49–1), which was lower than those who were inactive in multivariable analysis with mutual adjustments for other physical activity types. This falls within the CI for all-cause mortality reduction among patients with diabetes who were highly physically active (29%, 95% CI 44–8) compared with those who were inactive, as reported by Hu et al. (11),

in a multivariate analysis with mutual adjustments for other physical activity types. Conversely, the lack of an association between sports/exercise and CVD mortality in our study may be due to the low number of events (only 17 deaths) and resultant broad CIs.

Our data on the protective effects of walking for all-cause and CVD mortality are consistent with recent literature (8–10,34,35). However, most previous studies have examined the effects of higher doses of walking. For example, in a previous study (9) individuals who walked ≥2 h/week had a 39% lower risk of all-cause mortality (22–52%) and a 44% lower risk of CVD mortality (4–55%) compared with those reporting no walking. Another study (10) found that diabetic patients classified in the top quintile (≥16.1 MET-hours/week) of walking from a large U.S. cohort had a 43% lower risk of all-cause mortality (17–41%). Our results expand on these findings by suggesting that, even when other physical activity is taken into account, low doses of walking (0.1–5.3 MET-hours/week, corresponding roughly to 1.5–1.7 h of walking) were still beneficially associated with

all-cause mortality among male patients with diabetes.

Overall, moderate physical activity (0.1–7.4 MET-hours/week, which is below the recommended amounts) in a diabetic population would still be beneficial to reduce all-cause and CVD mortality.

This is, to our knowledge, the first study to examine the associations of domestic physical activity with all-cause and CVD mortality in a population sample of patients with diabetes. Our results are in partial agreement with previous general population studies (23,28) as we found no evidence for a dose-response association between domestic physical activity and all-cause and CVD mortality (28), although the group classified as below the sex-specific median showed 27% lower risks of all-cause mortality (9–41%) compared with the reference group. Reasons for this finding could be due to differences in the intensity at which these activities are performed (not sensitive to interindividual differences) and problems within the questionnaire capturing not only moderate-intensity activities but also

light activities, diluting the true association.

Assuming the associations that we and others (15) have observed are causal, health practitioners should encourage diabetic patients to engage in physical activity. Furthermore, clinical and public health guidelines for the management of diabetes should incorporate regular physical activity.

The mechanisms by which physical activity reduces all-cause and CVD mortality among patients with diabetes have been proposed in several previous studies (16–21). Improved insulin sensitivity and glycemic control are mechanisms that benefit patients with diabetes through an increased rate of GLUT4s and glycogen synthase, in addition to hypertrophy of type I fibers, neovascularization, and an increase in muscle mass (16–21,35). Another mechanism could be the lower levels of free fatty acids and the increase in adiponectin with participation in physical activity (17–19). In addition, regular physical activity in patients with diabetes is associated with a reduction in other CVD risk factors, such as blood pressure (16,17) and adiposity (17), among many others.

Our study has several strengths and limitations. One of the key strengths of this study is the nationally representative population of pooled cohorts of people with typical characteristics of diabetes (i.e., higher BMI and presence of limiting long-standing illness) from England and Scotland. This diversity enhances the validity when making inferences to the overall diabetic population. Second, the availability of data on key physical activity domains, such as sports/exercise, walking, and domestic physical activities, adds to the novelty of these analyses. Finally, the inclusion of an objective criterion used to diagnose diabetes (HbA_{1c} level) allowed for more complete ascertainment of diabetes than relying on self-reported data alone, which would have excluded undiagnosed cases.

Limitations include the use self-reported physical activity measures that are subject to recall bias and over-reporting, increasing the possibility of

exposure misclassification. This might have led to a higher number of individuals meeting the physical activity recommendations, thus diluting the associations. Nevertheless, questionnaires are one of the most common tools for physical activity assessment in large epidemiologic studies (9,13,14,34), are the measurement tool on which health-based recommendations have been made, and showed good criterion validity (against accelerometry) in a general population sample of 107 English adults (36).

Second, reverse causality is likely to have overestimated the mortality risks if comorbidities at baseline led to inactivity. In the current study, adjustments were made for baseline diseases to minimize the chances of reverse causation (to maintain the sample size), as models were adjusted for existing CVD and limiting long-standing illness. Moreover, sensitive analyses were performed among subgroups to ascertain that the findings were not confounded by behaviors that may have changed as a result of a diagnosis. Finally, residual confounding cannot be ruled out; however, this study examined the potential effect of a large set of confounders. Moreover, we were able to make mutual adjustments for other activity types, minimizing the chances of residual confounding from other physical activities in the analyses.

In conclusion, our study provides evidence for an inverse association among total nonoccupational physical activity, walking, and sports/exercise, with risk of all-cause mortality in participants with diabetes. An inverse association between physical activity levels and CVD mortality was also present. However, there was no association between domestic physical activity and CVD mortality. Lifestyle activities such as walking might be effective in managing diabetes, yet are also easily incorporated into everyday life without the need for supervised exercise.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–321

2. Holt TA, Stables D, Hippisley-Cox J, O'Hanlon S, Majeed A. Identifying undiagnosed diabetes: cross-sectional survey of 3.6 million patients' electronic records. Br J Gen Pract 2008;58:192–196

3. Hamer M, Kengne AP, Batty GD, Cooke D, Stamatakis E. Temporal trends in diabetes prevalence and key diabetes risk factors in Scotland, 2003-2008. Diabet Med 2011;28:595–598

4. PBS diabetes prevalence model phase 3 [Internet], 2008. York, U.K., Yorkshire and Humber Public Health Observatory. Available from http://www.ntac.nhs.uk/web/FILES/InsulinInfusion/nhs__1276775255_31.PBS_Diabetes_Prevalence_Mod.pdf. Accessed 29 April 2013

5. Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 2001;161:1717–1723

6. Berry J, Keebler ME, McGuire DK. Diabetes mellitus and cardiovascular disease. Pandora's box has been opened. Herz 2004;29:456–462

7. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000;132:605–611

8. Batty GD, Shipley MJ, Marmot M, Smith GD. Physical activity and cause-specific mortality in men with type 2 diabetes/impaired glucose tolerance: evidence from the Whitehall study. Diabet Med 2002;19:580–588

9. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med 2003;163: 1440–1447

10. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003;107:2435–2439

11. Hu G, Eriksson J, Barengo NC, et al. Occupational, commuting, and leisure-time physical activity in relation to total and cardiovascular mortality among Finnish subjects with type 2 diabetes. Circulation 2004;110:666–673

12. Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005;28:799–805

13. Jonker JT, De Laet C, Franco OH, Peeters A, Mackenbach J, Nusselder WJ. Physical activity and life expectancy with and without diabetes: life table analysis of the Framingham Heart Study. Diabetes Care 2006;29:38–43

14. Nelson KM, Boyko EJ, Koepsell T. All-cause mortality risk among a national sample of individuals with diabetes. Diabetes Care 2010;33:2360–2364

15. Sluik D, Buijsse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. Arch Intern Med 2012; 172:1285–1295

16. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002;25:2335–2341

17. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care 2002;25:1729–1736

18. Cauza E, Hanusch-Enserer U, Strasser B, et al. The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. Arch Phys Med Rehabil 2005;86:1527–1533

19. Brooks N, Layne JE, Gordon PL, Roubenoff R, Nelson ME, Castaneda-Sceppa C. Strength training improves muscle quality and insulin sensitivity in Hispanic older adults with type 2 diabetes. Int J Med Sci 2007;4:19–27

20. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007;147:357–369

21. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011;305:1790–1799

22. Physical Activity Team, Department of Health. Start Active, Stay Active: A Report on Physical Activity From the Four Home Countries' Chief Medical Officers [Internet], 2011. London, Department of Health. Available from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216370/dh_128210.pdf. Accessed 3 December 2013

23. Stamatakis E, Hillsdon M, Primatesta P. Domestic physical activity in relationship to multiple CVD risk factors. Am J Prev Med 2007;32:320–327

24. Mindell J, Biddulph JP, Hirani V, et al. Cohort profile: the health survey for England. Int J Epidemiol 2012;41:1585–1593

25. Gray L, Batty GD, Craig P, et al. Cohort profile: the Scottish health surveys cohort: linkage of study participants to routinely collected records for mortality, hospital discharge, cancer and offspring birth characteristics in three nationwide studies. Int J Epidemiol 2010;39:345–350

26. Scottish Health Survey Team. Scottish Health Survey Design [Internet], 2013. Edinburgh, U.K., The Scottish Government. Available from http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey/SurveyDesignContent. Accessed 3 December 2013

27. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334

28. Stamatakis E, Hamer M, Lawlor DA. Physical activity, mortality, and cardiovascular disease: is domestic physical activity beneficial? The Scottish Health Survey—1995, 1998, and 2003. Am J Epidemiol 2009;169:1191–1200

29. Health and Social Care Information Center. Health Survey for England 2008: Methods and Documentation. In Health Survey for England 2008. Vol. 2. Leeds, U.K., Health and Social Care Information Center, 2009

30. British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005;91(Suppl. 5):1–52

31. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43: 1575–1581

32. Williams ED, Stamatakis E, Chandola T, Hamer M. Physical activity behaviour and coronary heart disease mortality among South Asian people in the UK: an observational longitudinal study. Heart 2011;97:655–659

33. Lee IM, Djoussé L, Sesso HD, Wang L, Buring JE. Physical activity and weight gain prevention. JAMA 2010;303:1173–1179

34. Smith TC, Wingard DL, Smith B, Kritz-Silverstein D, Barrett-Connor E. Walking decreased risk of cardiovascular disease mortality in older adults with diabetes. J Clin Epidemiol 2007;60:309–317

35. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007;30:744–752

36. Health and Social Care Information Center. Health Survey for England 2008: Physical Activity and Fitness. In Health Survey for England 2008. Vol. 1. Leeds, U.K., Health and Social Care Information Center, 2009