Reduced Total and Cause-Specific Mortality from Walking and Running in Diabetes

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ABSTRACT

WILLIAMS, P. T. Reduced Total and Cause-Specific Mortality from Walking and Running in Diabetes. *Med. Sci. Sports Exerc.*, Vol. 46, No. 5, pp. 933–939, 2014. **Purpose**: This study aimed to assess the relationships of running and walking to mortality in diabetic subjects. **Methods**: We studied the mortality surveillance between January 1, 1989 and December 31, 2008, of 2160 participants of the National Walkers' and Runners' Health Studies who reported using diabetic medications at baseline. Hazard ratios (HR) and 95% confidence intervals (95% CI) were obtained from Cox proportional hazard analyses for mortality versus exercise energy expenditure (MET-hours per day, 1 MET·h ~1-km run or a 1.5-km brisk walk). **Results**: Three hundred and thirty-one diabetic individuals died during a 9.8-yr average follow-up. Merely meeting the current exercise recommendations was not associated with lower all-cause mortality (P = 0.61), whereas exceeding the recommendations was associated with lower all-cause mortality (HR = 0.64, 95% CI = 0.49–0.82, P = 0.0005). Greater MET-hours per day ran or walked was associated with 40% lower risk for all chronic kidney disease-related deaths (HR = 0.60 per MET·h·d^{-1}, 95% CI = 0.35–0.91, P = 0.02), 31% lower risk for all sepsis-related deaths (HR = 0.69, 0.47–0.94, P = 0.01), and 31% lower risk for all pneumonia and influenza-related deaths (HR = 0.69, 95% CI = 0.45–0.97, P = 0.03). Running or walking ≥1.8 MET·h·d^{-1} was associated with 57% reduction in cardiovascular disease (CVD) as an underlying cause of death and 46% lower risk for all CVD-related deaths versus <1.07 MET·h·d^{-1}. All results remained significant: 1) adjusted for baseline BMI and 2) excluding all deaths within 3 yr of baseline. **Conclusions**: These results suggest that 1) exercise is associated with significantly lower all-cause, CVD, chronic kidney disease, sepsis, and pneumonia, and influenza mortality in diabetic patients and 2) higher exercise standards may be warranted for diabetic patients than currently provided to the general population. **Key Words:** PHYSICAL ACTIVITY, CHRONIC KIDNEY DISEASE, PREVENTION, COHORT, SEPSIS, CARDIOVASCULAR DISEASE

Diabetes is the leading cause of kidney failure in the United States (29). In addition, diabetic patients are at increased risk for peripheral and autonomic neuropathy, silent ischemia, cardiac arrhythmias, and increased risk for sudden death (22). They are also at a greater risk of dying from pneumonia or influenza compared with individuals without diabetes (29). The risk for cardiovascular disease (CVD) mortality is greatest among those diabetic patients treated with oral hypoglycemic drugs or insulin (1,3).

Public health guidelines for adults between 18 and 65 yr old recommend "at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity" (25). A somewhat greater exercise dose has been recommended specifically for patients with type 2 diabetes, that is, "at least 150 min/week of moderate to vigorous aerobic exercise spread out during at least 3 d during the week, with no more than two consecutive days between bouts of aerobic activity" (2). Exercise helps prevent impaired glucose tolerance from developing into diabetes (2) and improves insulin sensitivity and glycemic control in diabetic patients (2). There is substantial evidence showing that exercise improves CVD risk factors and lowers CVD and all-cause mortality in diabetic patients (8,11,12,28,32), but there are few details regarding the specific CVD diagnoses affected. Whether exercise lowers the risk of chronic kidney disease, sepsis, and respiratory disease in diabetic patients is not known.

This report examines the dose–response relationship of running and walking to all-cause and cause-specific mortality in 2160 patients who reported taking medications for diabetes in the National Walkers' and Runners' Health Studies (33–36). Specifically, the goals of the analyses were 1) to test whether running and walking significantly reduce the risks for chronic kidney disease, sepsis, and influenza and pneumonia-related deaths and 2) to confirm the reduction in all-cause and CVD-related deaths with increased exercise as has been reported by others (8,11,12,28,32), and 3) to assess whether the exercise standards for diabetic patients are sufficient (2).

METHODS

The National Walkers' and Runners' Health Studies have been described in detail (33–36). Walkers were recruited between 1999 and 2001, whereas runners were recruited in two

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waves, between 1991 and 1993 (phase I) and between 1998 and 2001 (phase II), through the solicitation of subscribers of activity-targeted publications and participants at footrace events. The study protocol was approved by the University of California Berkeley committee for the protection of human subjects, and all subjects provided a signed statement of informed consent.

Participants completed a four-page survey on running and walking history, height, weight, diet, smoking, and history of diseases. Diabetic patients were identified as those subjects who reported using medications for diabetes at baseline. Intakes of meat and fruit were based on the questions "During an average week, how many servings of beef, lamb, or pork do you eat," and "During an average week, how many pieces of fruit do you eat." Alcoholic beverage consumption was ascertained from the corresponding questions for 4-oz (112 mL) glasses of wine, 12-oz (336 mL) bottles of beer and mixed drinks and liqueurs, and alcohol intake was estimated from 10.8 g per 4-oz glass of wine, 13.2 g per 12-oz bottle of beer, and 15.1 g per mixed drink. Distance run was obtained from the question "Average miles run per week for" and then listed the current and preceding 5 yr with spaces for the responses (the most recent distance was used for analyses). Pace was determined by the question "During your usual run, how many minutes does it take for you to run one mile?" Walking distance and pace were ascertained using the same questions for walking instead of running. Running and walking energy expenditure was expressed in units of METs, in which one MET is the energy expended sitting at rest (3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) (25). Running MET values were calculated as 1.02 $MET \cdot h \cdot km^{-1}$ (35). Walking energy expenditure ($MET \cdot h \cdot d^{-1}$) was computed by converting the reported usual weekly distance into duration (i.e., distance divided by mph) and then calculating the product of the average hours walked per day and the MET value corresponding to their reported pace (36).

Mortality surveillance was completed through 2008 using the National Death Index plus (23), which provides cause-specific mortality (*International Classification of Diseases, Ninth Revision* [ICD-9] and *International Classification of Diseases, 10th* [ICD-10] [39]) for both underlying and contributing (entity axis) causes of death. The underlying cause of death is the disease or injury that initiated the chain of morbid events that led directly and inevitably to death. Other contributing causes of death are all other significant diseases, conditions, or injuries that contributed to death but which did not result in the underlying cause of death. "All-related" mortality refers to whether a particular cause of death was listed anywhere on the certificate (i.e., underling or contributing). Cox proportional hazard analyses (JMP version 5.1; SAS Institute, Cary, SC) were used to test whether total and cause-specific mortality were significantly related to MET-hours per day ran or walked when adjusted for baseline age (age and age^2), sex, years of education, baseline smoking status (current smoker vs nonsmoker), cohort (phase I runner, phase II runner, and walker), and intakes of meat, fruit, and alcohol. Additional adjustment for BMI was included where indicated. Results are presented as hazard ratios (HR) and their percent increase or decrease in risk (calculated as 100 [HR − 1]) per MET-hours per day ran or walked, and for categories of exercise energy expenditure: 1) falling short of the current exercise recommendations for health (<450 $MET \cdot min \cdot wk^{-1}$ = 1.07 $MET \cdot h \cdot d^{-1}$ [10]), 2) achieving the exercise recommendations (450–750 $MET \cdot min \cdot wk^{-1}$ = 1.07–1.8 $MET \cdot h \cdot d^{-1}$ [10]), and 3) exceeding the recommendations. The attenuation of the risk reduction at higher exercise dose was tested formally by including both MET-hours per day and MET-hours per day squared as independent variables in the survival model. A nonsignificant positive quadratic term (i.e., MET-hours per day squared = 0) would suggest a continuing proportional decline in mortality as described by the linear term, whereas a significant positive quadratic term (i.e., MET-hours per day squared ≠ 0) would suggest that at higher exercise doses, there is a diminished risk reduction as higher exercise doses (i.e., a leveling off of the risk reduction). All analyses exclude deaths that occurred within 1 yr of the baseline survey and within 3 yr of baseline where indicated.

RESULTS

There were 331 deaths during (mean ± SD) 9.84 ± 2.33 yr of follow-up in the 2160 patients (1601 walkers, 559 runners) who reported using diabetic medications at baseline. These included 125 deaths due to CVD (ICD-10: I00–I99), 77 due to malignant neoplasms (ICD-10: C00–C97), 36 due to diabetes mellitus (ICD-10: E10–E14), 26 due to respiratory diseases (ICD-10: J00–J98), 14 due to accidents and external causes (ICD-10: V00–Y98), 11 due to digestive diseases (ICD-10: K00–K92), 9 due to infectious and parasitic diseases (ICD-10: A00–B99), 8 due to mental and behavioral disorders (ICD-10: F01–F99), 6 due to systemic atrophies primarily affecting the central nervous system (ICD-10: G00–G98), 6 due to genitourinary diseases (ICD-10: N00–N98), and 13 due to other underlying causes of death.

Relative to the 153,324 nondiabetics of the original cohort, the 2160 diabetic individuals were at 94.2% greater risk for mortality due to all causes (HR = 1.942, 95% confidence interval [CI] = 1.729–2.181, $P < 10^{-15}$), 2-fold greater risk for CVD as underlying cause (HR = 2.019, 95% CI = 1.668–2.444, $P < 10^{-15}$), 2.2-fold greater risk for all CVD-related deaths (HR = 2.234, 95% CI = 1.928–2.589, $P < 10^{-15}$), 25-fold greater risk for diabetes as an underlying cause (HR = 24.874, 95% CI = 14.396–43.436, $P < 10^{-15}$), 3-fold greater risk for all sepsis-related deaths (HR = 2.988, 95% CI = 1.916–4.492, $P = 10^{-5}$), 5.4-fold greater risk for deaths involving chronic kidney disease (HR = 5.410, 95% CI = 2.961–9.523, $P < 10^{-6}$), and 64% greater risk for deaths involving pneumonia or influenza (HR = 1.636, 95% CI = 1.019–2.498, $P = 0.04$). The baseline characteristics of the diabetic subjects by vital status and exercise energy expenditure are displayed in Table 1. Those who died were more likely to be male, older, walkers, slightly less educated, and to have

TABLE 1. Baseline characteristics (mean ± SD or percent) of the sample.

	Walking or Running Energy Expenditure					
	<1.07 MET·h·d^{-1}		1.07–1.8 MET·h·d^{-1}		≥1.8 MET·h·d^{-1}	
	Dead	Alive	Dead	Alive	Dead	Alive
Sample	162	626	57	276	112	927
Male (%)	52.47	44.50	59.65	38.41	75.00	54.69
Runners (%)	8.64	15.33	5.26	13.04	29.46	40.67
Prior heart attack (%)	25.93	10.22	28.07	9.42	22.32	5.39
White (%)	76.54	71.41	87.72	79.71	83.04	84.25
Age (yr)	70.19 ± 12.08	57.51 ± 13.01	69.41 ± 12.23	55.60 ± 12.58	66.18 ± 13.17	53.30 ± 13.25
Education (yr)	13.90 ± 2.68	14.59 ± 2.68	14.52 ± 2.79	14.97 ± 2.61	15.05 ± 2.68	15.45 ± 2.66
Meat (servings per day)	0.47 ± 0.43	0.55 ± 0.49	0.59 ± 0.48	0.48 ± 0.39	0.52 ± 0.51	0.45 ± 0.40
Fruit (pieces per day)	1.38 ± 1.05	1.41 ± 1.08	1.75 ± 1.09	1.67 ± 1.42	1.67 ± 1.09	1.77 ± 1.27
Alcohol (g·d^{-1})	4.34 ± 13.59	3.49 ± 10.25	3.34 ± 9.29	3.64 ± 7.42	6.40 ± 11.49	5.97 ± 12.14
Aspirin use (tablets per day)	0.54 ± 0.82	0.44 ± 0.74	0.46 ± 0.61	0.44 ± 0.75	0.48 ± 0.51	0.43 ± 0.73
Body mass index (kg·m^{-2})	30.53 ± 8.40	31.57 ± 7.65	29.51 ± 6.91	29.98 ± 6.87	27.52 ± 5.87	27.08 ± 5.66

had a prior heart attack. The analyses to follow include sex, age (age, age^2), race, exercise mode, education, prior heart attack, baseline smoking, and intakes of meat, fruit, alcohol, and aspirin as covariates.

Total mortality. The relationship of total mortality to MET-hours per day ran or walked was significantly nonlinear, with most of the reduction in risk having occurred by 1.8–3.6 MET·h·d^{-1} (not displayed). Nonlinearity was confirmed the significance quadratic coefficient of the regression model (Table 2). Meeting the current exercise recommendation was associated with a nonsignificant 7.5% reduction in mortality, whereas exceeding the recommendations was associated with a significant 36.5% risk reduction for all-cause mortality (Table 2). Adjustment for BMI slightly attenuated the risk reduction associated with exceeding the recommendations (HR = 0.711 per MET-hour per day, 95% CI = 0.537–0.937, P = 0.02).

CVD—Underlying cause. There was a 40.3% reduction in CVD mortality by achieving the recommended activity level (P = 0.05) and a 57.1% reduction by exceeding it (P = 0.0001). Nearly two-thirds of the deaths were ascribed to ischemic heart disease, and although the 1.07- to 1.8-MET·h·d^{-1} category and the ≥1.8-MET·h·d^{-1} category did not differ individually from <1.07 MET·h·d^{-1} with statistical significance, there was a 37.6% risk reduction for ischemic heart disease mortality versus those that ran or walked less when combined (i.e., ≥1.07 vs. <1.07 MET·h·d^{-1}; HR = 0.624, 95% CI = 0.394–0.986, P = 0.04). The 43 remaining

TABLE 2. HR (95% CI) for total and cause-specific mortality versus MET-hours per day walked or ran in 2160 diabetic participants of the National Walkers' and Runners' Health Studies.

	Categorical Model, i.e., HR for Categories of MET-Hours per Day Ran or Walked Relative to <1.07 MET·h·d^{-1}		Continuous Model, i.e., Reduction in Risk per MET-Hours per Day Walked or Ran	
	1.07–1.8 MET·h·d^{-1}	≥1.8 MET·h·d^{-1}	Linear (MET·h·d^{-1})	Quadratic (MET·h·d^{-2})[a]
Total mortality	0.925 (0.676, 1.247), P = 0.61	0.635 (0.489, 0.821), P = 0.0005	0.860 (0.797, 0.927), P = 0.0001	1.012 (1.005, 1.018), P = 0.003
Underlying				
CVD (ICD-10, I00–I99), 125 deaths	0.597 (0.339, 0.991), P = 0.05	0.429 (0.275, 0.656), P = 0.0001	0.770 (0.671, 0.876), P = 0.0001	1.017 (1.002, 1.027), P = 0.03
Ischemic heart disease (ICD-10, I20–I25), 82 deaths	0.535 (0.243, 1.055), P = 0.07	0.663 (0.399, 1.088), P = 0.10	0.880 (0.755, 1.016), P = 0.08	1.011 (0.991, 1.021), P = 0.20
Other CVD, 43 deaths	0.666 (0.282, 1.340), P = 0.30	0.121 (0.035, 0.318), P = 0.0001	0.523 (0.374, 0.697), P = 0.0001	1.036 (0.957, 1.057), P = 0.22
All related deaths				
CVD (ICD-10, I00–I99), 213 deaths	0.762 (0.507, 1.115), P = 0.17	0.541 (0.389, 0.745), P = 0.0002	0.818 (0.741, 0.899), P = 0.0001	1.016 (1.009, 1.022), P = 0.0003
Ischemic heart disease (ICD-10, I20–I25), 120 deaths	0.547 (0.294, 0.949), P = 0.03	0.589 (0.385, 0.890), P = 0.01	0.818 (0.741, 0.899), P = 0.0001	1.016 (1.009, 1.022), P = 0.0003
Dysrhythmias (ICD-10, I46–I49), 72 deaths	0.493 (0.200, 1.053), P = 0.07	0.705 (0.415, 1.190), P = 0.19	0.917 (0.786, 1.062), P = 0.25	1.010 (0.994, 1.020), P = 0.18
Heart failure (ICD-10, I20), 72 deaths	1.683 (0.814, 3.349), P = 0.15	0.395 (0.170, 0.859), P = 0.02	0.748 (0.587, 0.929), P = 0.008	1.022 (0.990, 1.037), P = 0.12
Cerebrovascular disease (ICD-10, I60–I69), 32 deaths	0.622 (0.179, 1.674), P = 0.04	0.448 (0.177, 1.031), P = 0.06	0.789 (0.591, 1.014), P = 0.07	1.028 (1.013, 1.045), P = 0.0006
Hypertensive disease (ICD-10, I10–I13), 50 deaths	1.048 (0.495, 2.075), P = 0.90	0.356 (0.167, 0.716), P = 0.003	0.720 (0.575, 0.881), P = 0.001	1.020 (0.983, 1.035), P = 0.19
Sepsis (ICD-10, A40–A41), 27 deaths	Not estimated	Not estimated	0.658 (0.461, 0.892), P = 0.006	1.042 (0.965, 1.078), P = 0.19
Chronic kidney disease (ICD-10, N18), 18 deaths	0.170 (0.009, 0.867), P = 0.03	0.195 (0.042, 0.647), P = 0.006	0.576 (0.344, 0.873), P = 0.007	1.032 (0.943, 1.062), P = 0.29
Pneumonia and influenza (ICD-10, J10–J18), 22 deaths	0.743 (0.168, 2.364), P = 0.64	0.260 (0.067, 0.783), P = 0.02	0.685 (0.452, 0.961), P = 0.03	1.022 (0.857, 1.051), P = 0.67

Adjusted for baseline age (age and age^2), sex, years of education, baseline smoking status (current smoker vs nonsmoker), cohort (phase I runner, phase II runner, and walker), and intakes of meat, fruit, and alcohol.

[a]A nonsignificant quadratic term would suggest a continuing proportional decline in mortality as described by the linear term, whereas a significant positive quadratic term would suggest that there is a diminished risk reduction at higher exercise doses (i.e., a leveling off of the risk reduction).

nonischemic heart disease CVD deaths included 8 diagnoses of heart failure, 10 diagnoses of cerebrovascular disease, 6 diagnoses of dysrhythmias, 6 diagnoses of hypertensive disease, and 13 other underlying diagnoses. Expending ≥1.8 MET·h·d^{-1} was associated with a 87.9% reduction in their combined risk versus <1.07 MET·h·d^{-1}. Adjustment for BMI eliminated the significance decrease in CVD mortality for meeting the recommendations (HR = 0.694, 95% CI = 0.384–1.183, P = 0.19) but not for exceeding them (HR = 0.469, 95% CI = 0.291–0.738, P = 0.001).

All related CVD deaths. Two-thirds of the 331 deaths included CVD as either the underlying cause, or as contributing to the death for some other underlying cause of death. Collectively, the risk for all CVD-related mortality was 23.8% lower by running or walking 1.07–1.8 MET·h·d^{-1} (P = 0.17) and 45.9% lower by exceeding this level (P = 0.0002) versus inadequate exercise. The reduction in all ischemic heart disease-related deaths appeared to have been achieved by merely satisfying the recommendations, a 45.3% reduction for 1.07–1.8 MET·h·d^{-1} (P = 0.03), and a 41.1% reduction for ≥1.8 MET·h·d^{-1} (P = 0.01). The reduction in all dysrhythmia and all cerebrovascular-related deaths also appear to have occurred primarily by achieving the recommendation, albeit not significantly. Reductions in the risk for heart failure and hypertensive disease were more linear, that is, a 20.7% reduction per MET-hour per day for heart failure (HR = 0.793 per MET-hour per day, 95% CI = 0.622–0.975, P = 0.03) and a 25.0% reduction per MET-hour per day for hypertensive disease (HR = 0.750 per MET-hour per day, 95% CI = 0.598–0.912, P = 0.003) when the nonsignificant quadratic term was removed from the model.

Diabetes—Underlying cause. There was a linear reduction in risk for mortality with diabetes as the underlying cause (ICD-10, E10–E14). Its risk declined 22.1% per MET-hours per day ran or walked (HR = 0.779, 95% CI = 0.606–0.965, P = 0.02). Adjustment for baseline BMI somewhat weakened the significance of the risk decrease (HR = 0.833, 95% CI = 0.641–1.038, P = 0.10); however, this was due both to the smaller HR and the smaller sample size (31 deaths among 2035 patients with BMI values vs 36 deaths among all 2160 patients). Only 38.3% of the deaths listed diabetes as a contributing or underlying cause, and 80% of those that did also listed CVD as a cause of death.

Sepsis. Of the 27 sepsis-related deaths, 21 occurred in subjects who were inadequately exercising (<1.07 MET·h·d^{-1}), none occurred in those that merely met the recommendations, and 6 occurred in those that exceeded the recommendations The risk for sepsis decreased an average of 31.2% per MET-hour per day (HR = 0.688, 95% CI = 0.470–0.936, P = 0.01), which persisted when adjusted for BMI (HR = 0.644, 95% CI = 0.410–0.897, P = 0.01).

Chronic kidney disease. The risk for all chronic kidney disease-related deaths decreased 40% per MET-hour per day (HR = 0.600, 95% CI = 0.348–0.912, P = 0.01), which persisted when adjusted for BMI (HR = 0.600, 95% CI = 0.340–0.925, P = 0.02). When adjusted for BMI, the risk for chronic kidney disease was 80.1% lower (HR = 0.189, 95% CI = 0.010–0.982, P = 0.05) and 79.1% lower (HR = 0.209, 95% CI = 0.044–0.708, P = 0.01) in diabetic subjects who walked or ran 1.07–1.8 MET·h·d^{-1} and ≥1.8 MET·h·d^{-1} versus <1.07 MET·h·d^{-1}, respectively. Twelve of those who died were also on hypertensive medications at baseline; however, the risk reduction remained significant when adjusted for hypertensive medication use (HR = 0.608, 95% CI = 0.353–0.924, P = 0.02). Only one chronic kidney disease death did not list CVD as a contributing or underlying cause.

Pneumonia and influenza. The risk for pneumonia- or influenza-related deaths declined linearly with increasing MET-hours per day ran or walked (Table 2). Excluding the nonsignificant quadratic term, this corresponded to a 30.9% decline per MET-hours per day ran or walked (HR = 0.691, 95% CI = 0.447–0.965, P = 0.03) without adjustment for baseline BMI and a 44.0% decline per MET-hours per day ran or walked (HR = 0.560, 95% CI = 0.315–0.848, P = 0.003) when adjusted. Diabetic subjects who ran or walked ≥1.8 MET·h·d^{-1} were at 74% lower risk for pneumonia- or influenza-related mortality without adjusting for BMI (Table 2) and 83.4% lower risk when adjusted for BMI (HR = 0.116, 95% CI = 0.034–0.562, P = 0.003). When the 10 CVD-related deaths were excluded, the risk for pneumonia-or influenza-related deaths declined 31.7% per MET-hour per day (HR = 0.683, 95% CI = 0.347–1.079, P = 0.12) and was 85.1% lower for diabetic subjects that ran or walked ≥1.8 MET·h·d^{-1} versus <1.07 MET·h·d^{-1} (HR = 0.149, 95% CI = 0.008–0.849, P = 0.03).

Other causes of death. Eighty-seven of the 331 deaths did not have diabetes as their underlying cause of death and were not related to CVD, sepsis, chronic kidney disease, or pneumonia or influenza. Their risk was unrelated to MET-hours per day ran or walked (HR = 0.977 per MET-hour per day, 95% CI = 0.860–1.093, P = 0.70).

Further exclusion of early mortality. There were 73 deaths during the first 3 yr of follow-up; their exclusion leaves 2087 diabetic subjects who did not die within 3 yr of their baseline visit. Compared with <1.07 MET·h·d^{-1}, diabetic subjects who ran or walked ≥1.8 MET·h·d^{-1} were at 34.3% lower risk for all-cause mortality (P = 0.004, 258 deaths), 52.8% lower risk for CVD as an underlying cause (P = 0.003, 92 deaths), 45.1% lower risk for all CVD-related mortality (P = 0.004, 165 deaths), 38.6% lower risk for all ischemic heart disease-related mortality (P = 0.04, 91 deaths), and 61.0% lower risk for all cerebrovascular disease-related mortality (P = 0.09. 20 deaths). Each MET-hours per day ran or walked was associated with a 22.6% reduction in all heart failure–related mortality (P = 0.03, 35 deaths), a 22.7% reduction in all hypertensive disease-related mortality (P = 0.02, 39 deaths), a 21.8% reduction in diabetes as an underlying cause of death (P = 0.03, 33 deaths), a 33.2% reduction in all sepsis-related mortality (P = 0.02, 22 deaths), a 37.3% reduction in all chronic kidney disease-related deaths (P = 0.02, 16 deaths), and a 39.2%

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reduction in all pneumonia and influenza-related deaths (P = 0.02, 16 deaths).

DISCUSSION

Compared with other runners and walkers, those that reported taking medications for diabetes were at significantly greater risk for mortality due to all causes, diabetes, and CVD as underlying causes of death and all mortality related to CVD, sepsis, chronic kidney disease, and pneumonia and influenza (underlying or contributing). Although the beneficial effects of exercise on mortality due to all causes and CVD are well established in diabetic patients, reductions in sepsis, chronic kidney disease, and pneumonia and influenza are not. Our analyses show that greater MET-hours per day ran or walked was associated with clinically and statistically significant reduction in mortality involving sepsis, chronic kidney disease, and pneumonia and influenza, and that these risk reductions were significant even excluding those deaths involving CVD. Our analyses also confirm the reduction in all-cause and CVD mortality with exercise in diabetic patients and the need for diabetic patients to exceed the public health recommendations for physical activity for the general population of adults. Specifically, significant reductions in total mortality in diabetic patients were observed for ≥1.8 MET·h·d^{-1} but not for 1.07–1.8 MET·h·d^{-1}. Exceeding 1.8 MET·h·d^{-1} corresponds to approximately 200 min·wk^{-1} of brisk walking or approximately 100 min of running at a 13-min mile, or if done in equal proportions, 150 min of moderate and vigorous exercise per week, as recommended for diabetic patients (2).

Chronic kidney disease. Physical activity is not currently recognized as a hygienic approach to lowering chronic kidney disease risk (25). We have previously reported that running and walking were associated with 25.4% per MET-hour per day reduction in chronic kidney disease mortality in hypertensives, independent of both diabetes and BMI (37). Hypertension and diabetes are related conditions, that is, hypertensives are 2.5-fold more likely to develop diabetes within 5 yr than normotensives (9,27), and treating insulin resistance often lowers blood pressure (30). Both diseases are recognized risk factors for chronic kidney disease (16); however, the reduction in chronic kidney disease with running and walking was significant when adjusted for baseline hypertensive medication use, suggesting that the reduction in risk was not simply due to the antihypertensive effects of running and walking in these cohorts (33,34). The current analyses provide a second report for a significant reduction in chronic kidney disease mortality with exercise in patients at risk for the disease.

Pneumonia, influenza, and sepsis. Type 2 diabetes is associated with an increased susceptibility to infection and sepsis that is probably due to neutrophil defects arising from hyperglycemia, and possibly defects in humoral immunity (14). Nearly one-half of all diabetic patients require medical intervention for infections annually (26). Diabetes mellitus is associated with a higher risk of death after community-acquired pneumonia (40) but may not be a risk factor for nosocomial pneumonia or mortality arising from nosocomial infection (31).

The approximately 30% reduction in mortality due to influenza, pneumonia, or sepsis per MET-hours per day ran or walked suggests potentially substantial cost savings from exercise promotion if the effects are causal. These reductions in mortality could be due to improved immunoresponsiveness, improved efficacy of vaccinations to prevent infections or minimize disease severity, or the co-segregation of health behaviors (i.e., greater distance ran or walked serving as a marker for patients more likely to pursue influenza and pneumococcal vaccinations). They contradict the hypothesis, at least in diabetic patients, that acute strenuous and prolonged exercise increases the vulnerability to upper respiratory tract and other infections due to suppression of the immune system (24). In fact, aerobic exercise training has been shown to decrease plasma C-reactive protein, tumor necrosis factor α, and interleukin 1α/interleukin 10 ratios in patients with type 2 diabetes (13). In nondiabetic patients, both chronic (6,15,38) and acute bouts exercise (5) are reported to improve antibody responses to vaccination.

All-cause and CVD mortality. Our results appear entirely consistent with other research that shows that physical activity lowers all-cause and CVD mortality. Gregg et al. (8) reported that diabetic patients who walked 2 h·wk^{-1} were at 39% lower all-cause mortality and a 34% lower CVD mortality compared with inactive diabetic patients during the 8-yr follow-up of the 1991 National Health Interview Survey. Diabetic subjects that walked 3–4 h·wk^{-1} had 54% reduction in all-cause mortality and 53% reduction in CVD mortality relative to inactive diabetic patients (8). Hu et al. (11) reported that the incident CVD risk in diabetic women decreased 7% for exercising at moderate or vigorous intensity 1–2 h·wk^{-1}, 18% for 2–4 h·wk^{-1}, 46% for 4–7 h·wk^{-1}, and 48% for ≥7 h·wk^{-1} relative to <1 h·wk^{-1} and that incident CVD risk declined in association with walking in women who did not exercise vigorously. The highest quintile of walking was associated with 43% lower risk of total mortality compared with the lowest quintile in male diabetic participants of the Health Professionals' Follow-up Study (28). Analyses by Wei et al. (32) showed that diabetic subjects who had low cardiorespiratory fitness or who were physically inactive were at 2.1- and 1.7-fold greater risk for all-cause mortality, respectively, than those who were fit or physically active. Lower total and CVD mortality were also reported for moderately or highly active Finnish patients with type 2 diabetes versus those less active (12).

Diabetes. The results for diabetes underscore the problems with death certificate diagnoses in general, and with restricting the analyses to underlying causes of death in particular. The underlying cause of death is defined by the World Health Organization as "the disease or injury which initiated the train of morbid events leading directly to death" (39). Twenty-nine of the 36 deaths that listed diabetes as the underlying cause included CVD as a contributing cause, and 80% of deaths that listed diabetes as a contributing or underlying cause also included CVD on the death certificate. Although all of the participants reported taking diabetes medication at baseline, only 38% listed diabetes anywhere on the death certificate, which is essentially identical with the 39% reported for the translating research into action for diabetes study (19) and other articles cited therein. Whether diabetes is listed on the death certificate at all may reflect the familiarity of the certifying physician with the patient medical history (e.g., 70% by personal physician vs 29% for other physician [20]), and whether it is listed as the underlying cause may depend on whether the certifying physician is an endocrinologist, cardiologist, or nephrologist (17). The concomitant increase in diabetes and decrease in CVD as underlying causes of death between 2000 and 2007 in the United States may illustrate, in part, the effect of increasing media attention on diabetes on death certificate diagnoses (18).

Reverse causality. Reverse causality is an important consideration in interpreting the associations between mortality and physical activity reported here and by others. Specifically, microvascular and macrovascular diseases (4), falls, foot ulcers, and functional limitations due to the diabetic condition (7) could have limited running and walking at baseline. Diabetic patients 60 yr and older are two to three times more likely to be unable to walk a quartile mile, climb stairs, or perform housework as age-matched nondiabetic individuals (29). Our analyses specifically recruited subjects who walked or ran for exercise, which may have excluded at least some of those whose exercise is limited by diabetes. Traditionally, epidemiological studies exclude early mortality to assess the effects of reverse causality. In that regard, our analyses exhibited very little difference in the risk reductions when deaths occurring within 1 and 3 yr of baseline were excluded, that is, 36.5% versus 29.9% lower risk for total mortality, respectively; 45.9% versus 45.1% lower risk for all CVD-related mortality, respectively; 41.1% versus 38.6% lower risk for all ischemic heart disease-related mortality, respectively; 55.2% versus 61.0% lower risk for all cerebrovascular disease-related mortality, respectively; and 57.1% and 52.8% lower risk for CVD as an underlying cause, when comparing $\geq$1.8 to <1.07 MET·h·d^{-1}. Similarly, there was little difference when excluding the first year versus the first 3 yr of mortality for the per MET-hours per day reductions in diabetes as an underlying cause of death (22.1% vs 21.8%) and mortality related to all heart failure (20.7% vs 22.6%), all hypertensive heart disease (25.0% vs 22.7%), all sepsis (31.2% vs 33.2%), all chronic kidney disease (40.0% vs 37.3%), and all pneumonia and influenza (30.9% vs 39.2%, respectively).

Limitations. There are important limitations to these analyses. Diabetes medication use, exercise, and other baseline variables were from self-report from the participants' baseline questionnaires. It is not known whether these subjects have type 1 or type 2 diabetes. In addition, changes in these subject characteristics since baseline could have affected the subjects' risk. Diabetic patients were identified on the basis of their self-reported medication use, which would exclude diabetic subjects not taking medication and undiagnosed diabetes. We also acknowledge that runners and walkers who volunteer to participate in a national study of running and walking may differ from the general population; however, our results for all-cause and CVD mortality show strong agreement with nationally representative sample of Americans with diabetic subjects (8).

In conclusion, most people at risk for diabetes are not sufficiently active as defined by the recommendations for the general population, little less the recommendations for diabetic patients (21). These results identify important additional benefits for diabetic patients to exceed the current general physical activity recommendations for adults.

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EPIDEMIOLOGY

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