EXERCISE CAPACITY AND MORTALITY IN VETERANS WITH AND WITHOUT TYPE-2 DIABETES: AN ANALYSIS USING PROPENSITY MATCHING

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Abstract

Context. Recent studies have demonstrated a strong association between cardiorespiratory fitness (CRF) and mortality, but bias due to differences in the distribution of baseline variables has not been adequately considered. We studied a cohort of veterans with and without Type-2 diabetes using a propensity score matching method.

Methods. Males with (n=592) and without (n=6,167) Type-2 diabetes were studied. Propensity scores were used to balance covariate distributions between groups with and without Type-2 diabetes. All-cause mortality was the end point.

Results. Predictors of mortality included hypertension, smoking, Type-2 diabetes, BMI and CRF. For each 1 MET increase in CRF in the unmatched group, the adjusted HR was 0.83 in those with diabetes (95% CI 0.77-0.89; $p<0.0001$) compared to 0.87 in those without diabetes (95% CI 0.86-0.89; $p<0.0001$). Similar trends were observed for the matched dataset: the adjusted HRs were 0.83 (95% CI 0.77-0.90; $p<0.0001$) and 0.88 (95% CI 0.82-0.94; $p<0.0001$) for those with and without diabetes, respectively.

Conclusions. CRF is a strong predictor of mortality in veterans with and without Type-2 diabetes. Although the trend in the association between CRF and all-cause-mortality was similar for matched and unmatched data, the mortality risks were relatively inflated when using unmatched data.

Key words: Exercise capacity, Diabetes, Mortality, Exercise testing.

INTRODUCTION

Exercise capacity is a known predictor of mortality among healthy persons and those with cardiovascular disease (1, 2), but whether exercise capacity predicts mortality in persons with and without Type-2 diabetes has not been fully explored. Moreover, factors that increase mortality risk in Type-2 diabetes are not fully understood. This is potentially problematic

as understanding of excess mortality causes naturally precedes the development of effective interventions. Nevertheless, only a handful of recent reports have explored cause-specific mortality in this population (3, 4).

An established but rarely recognized factor in observational studies is the confounding by unmeasured or poorly measured variables at baseline. This creates a potential bias in which a factor (for example, diabetes) may be associated with an outcome, but it is not part of the causal pathway between the exposure and the outcome. A common cause of bias due to confounding is systematic differences in the distribution of baseline covariates between the treated and untreated subjects in an observational study (5). If these differences are significant, it may not be possible to compare outcomes between the treatment groups. The challenge for an observational study is finding an answer to the question regarding how the study would have been conducted if it were a controlled experiment. For example, in earlier studies focusing on diabetes, the stratified hazard ratios for all-cause mortality for those with and without diabetes were reported despite the fact that the two groups had differences in their baseline variable distributions. Researchers have used propensity score matching in order to replicate some of the conditions in randomized controlled experiments from observational studies. Similar to randomization in controlled experiments, propensity scoring removes the effect of confounding by forming groups of treated and untreated subjects having similar distributions of baseline covariates.

In the present study, we explored the relationship between exercise capacity and all-cause mortality in veterans with and without Type-2 diabetes. We used propensity score matching to balance the distribution of baseline variables between given pairs of subjects with and without Type-2 diabetes. Participants performed exercise testing for clinical reasons at the Veterans

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Affairs Medical Center in Palo Alto, California. The Veterans Health Administration in the U.S. Department of Veterans Affairs Health Care System is ideally suited for such follow-up studies because it ensures equal access to healthcare regardless of a patient's financial status (6). The electronic health information database maintained by the Veterans Affairs is well-suited for accurate mortality assessments (6), providing a means to determine the association between exercise capacity and mortality under similar medical conditions.

MATERIALS AND METHODS

Subjects and study design

We identified 6,759 veterans (age range, 45 to 70), 592 with and 6,167 without Type-2 diabetes who underwent a symptom-limited exercise tolerance test (ETT) at the Veterans Affairs Medical Center in Palo Alto, CA from 1986 and 2011, either as part of a routine evaluation or to assess exercise-induced ischemia. From this database, we excluded women ($\approx 3\%$ of the sample) and those with: 1) history of an implanted pacemaker; 2) left bundle branch block; 3) instability or need for emergency intervention; or 4) inability to complete the test because of musculoskeletal pain or impairments. All demographic, clinical, and medical information was obtained from the individual's computerized medical records prior to ETT. Each was asked to verify the computerized information, including history of chronic disease, current medications, and smoking habits. BMI was calculated as weight in kilograms divided by the square of height in meters. The study was conducted in accordance with the ethical standards approved by the institutional review board at Stanford University, and all subjects gave written informed consent before undergoing ETT.

Assessment of exercise capacity

Exercise capacity was assessed using an individualized ramp protocol as described previously (7). Exercise capacity (in METs) was estimated using standardized equations based on peak speed and grade. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping (8). Handrail use was discouraged but allowed only if needed for balance and safety. Medications were not altered before testing. Three fitness categories were established on the basis of the MET level achieved. Patients with a peak MET level ≤ 5.0 METs were classified as least fit; those with a

peak MET value between 5.1 and 10.0 were classified as moderately fit level; and those with a peak MET value >10.0 were classified as high fit.

Assessment of death

The primary outcome variable was all-cause mortality. The Veterans Affairs computerized medical records system was used to verify outcomes. Vital status was determined as of 30 July 2014.

Statistical analysis

STATA (11.2) software was used for all statistical analyses. Comparison of baseline characteristics between subjects with and without diabetes in the original sample along with propensity scores for the matched sample are shown in Table 1. The propensity score is "the conditional probability of receiving an exposure given a vector of measured covariates and is used to adjust for selection bias when assessing causal effects in observational studies." (9). We estimated the propensity score for having Type-2 diabetes for each patient using a multivariable logistic regression model, in which the presence of Type-2 diabetes was modeled using all baseline patient characteristics.

An established but rarely recognized factor in observational studies is the confounding by unmeasured or poorly measured variables at baseline. This creates a potential bias in which a factor (for example, diabetes) may be associated with an outcome, but it is not part of the causal pathway between the exposure and the outcome. A common cause of bias due to confounding is systematic differences in the distribution of baseline covariates between the treated and untreated subjects in an observational study (5). If these differences are significant, it may not be possible to compare outcomes between the treatment groups. The challenge for an observational study is finding an answer to the question regarding how the study would have been conducted if it were a controlled experiment. For example, in earlier studies focusing on diabetes, the stratified hazard ratios for all-cause mortality for those with and without diabetes were reported despite the fact that the two groups had differences in their baseline variable distributions. Researchers have used propensity score matching in order to replicate some of the conditions in randomized controlled experiments from observational studies. Similar to randomization in controlled experiments, propensity scoring removes the effect of confounding by forming groups of treated and untreated subjects having similar distributions of baseline covariates.

Table 1. Comparison of baseline characteristics between subjects with and without Type-2 diabetes in the unmatched and propensity score matched sample

Baseline Variable	Unmatched Data				Matched Data			
	W/o Diab.	With Diab.	Standardized	p*	W/o Diab.	With Diab.	Standardized	p*
	6167	592	Difference		480	480	Difference	
Age (years)	57.97 ± 11.59	61.16 ± 10.09	0.294	<0.001	60.42 ± 10.08	60.42 ± 10.08	0	0.986
Resting heart rate (beats/min)	75.71 ± 19.71	79.64 ± 30.45	0.153	<0.001	79.54 ± 43.57	78.3 ± 12.8	0.048	0.55
Resting systolic blood pressure (mm Hg)	132.29 ± 20.32	131.35 ± 18.06	0.049	0.28	133.06 ± 19.74	132.22 ± 18.10	0.045	0.48
Resting diastolic blood pressure (mm Hg)	81.57 ± 15.38	77.6 ± 10.08	0.305	<0.001	78.95 ± 11.49	78.4 ± 9.92	0.042	0.425
Peak heart rate (beats/min)	139.34 ± 25.35	135.58 ± 22.19	0.158	0.001	134.85 ± 22.74	134.94 ± 22.19	0.004	0.95
Peak systolic blood pressure (mm Hg)	176.86 ± 27.52	174.78 ± 26	0.078	0.077	175.1 ± 27.89	175.38 ± 26.13	0.01	0.88
Peak diastolic blood pressure (mm Hg)	85.09 ± 24.06	80.83 ± 13.55	0.218	<0.001	83.2 ± 14.56	81.7 ± 13.69	0.078	0.09
Peak Mets (3.5 ml O ₂ · kg ⁻¹ · min ⁻¹)	8.45 ± 4.13	7.23 ± 2.73	0.346	<0.001	7.22 ± 2.93	7.27 ± 2.71	0.014	0.78
BMI (kg/m ²)	30.23 ± 11.93	33.86 ± 14.32	0.275	<0.001	32.62 ± 13.15	32.92 ± 12.04	0.022	0.72
Hypertension	3037 (50.3%)	434 (76.1%)	0.563	<0.001	339 (70.63%)	350 (72.92%)	0.049	0.43
Family history of cardiovascular disease	1602 (26%)	117 (20%)	0.148	0.001	110 (22.92%)	101 (21.04%)	0.045	0.483
Current alcohol	226 (3.7%)	31 (5.2%)	0.076	0.072	23 (4.8%)	19 (4%)	0.04	0.528
Cholesterol	2241 (36.34%)	291 (49.16%)	0.261	<0.001	198 (41.3%)	215 (44.5%)	0.072	0.268
CVD	1592 (25.8%)	147 (24.8%)	0.023	0.6	133 (27.7%)	136 (28.3%)	0.014	0.83
Current smoking	545 (8.8%)	527 (89.02%)	2.684	<0.001	413 (86.04%)	415 (86.5%)	0.014	0.85
Ethnicity-African American	346 (5.61%)	19 (3.21%)	0.117	0.014	9 (1.9%)	16 (3.3%)	0.071	0.156
Ethnicity-White	4400 (71.35%)	370 (62.5%)	0.189	<0.001	308 (64.2%)	304 (63.3%)	0.018	0.788
Ethnicity-Other	1421 (23.04%)	203 (34.29%)	0.251	<0.001	163 (33.9%)	160 (33.3%)	0.014	0.83
~ Blocker	1333 (21.6%)	170 (28.7%)	0.164	0.001	137 (28.54%)	133 (27.77%)	0.019	0.774
Calcium channel blockers	1207 (20%)	112 (19.6%)	0.012	0.893	108 (22.5%)	95 (19.79%)	0.067	0.304
ACE inhibitors	1067 (17.3%)	382 (64.53%)	1.094	<0.001	243 (50.63%)	272 (56.67%)	0.14	0.061
Statins	667 (10.82%)	212 (35.81%)	0.618	<0.001	98 (20.42%)	105 (21.88%)	0.036	0.58
Diuretics	313 (5.08%)	86 (14.53%)	0.322	<0.001	48 (10%)	55 (11.46%)	0.05	0.465

Follow-up time is presented as median with interquartile ranges (IQRs). Mortality rate was calculated as the ratio of events by the number of persons or the person-years of observation. Continuous variables are presented as mean values ± SD and categorical variables as relative frequencies (percentages). Associations between categorical variables were tested using χ^2 analysis. One-way ANOVA and t-tests were applied to evaluate mean differences for normally distributed variables between groups. Equality of variances between groups was assessed using Levene's test. The assumption of normality was assessed using probability-probability plots.

Kaplan-Meier survival curves were generated for six fitness-diabetes categories using unmatched and matched datasets (Figs 2 and 3). Because of the assumption of independence between two data samples,

the log-rank test is not appropriate for comparing the Kaplan-Meier survival curves; instead, stratified log-rank test is used (9). Cox-proportional hazard models were used to determine variables that were significantly associated with mortality among these six categories. A Cox model with a robust variance estimator was used to account for the clustering within the matched sets (10). The group of high fit subjects without Type-2 diabetes (HighFit/NoDiab) was the reference group. The models were adjusted for age, body-mass index, ethnic origin, history of cardiovascular disease, cardiovascular medications (angiotensin-converting enzyme inhibitors, β blockers, calcium channel blockers, diuretics) and cardiovascular disease risk factors (hypertension, Type-2 diabetes mellitus, smoking, cholesterol, alcohol).

Figure 1. Standardized differences as a percentage for the unmatched and propensity score matched samples.

Figure 2. Kaplan-Meier survival estimates for the unmatched cohort.

Figure 3. Kaplan-Meier survival estimates for the propensity score matched cohort.

Table 2. Relative risk for all-cause mortality according to combined fitness and Type-2 diabetes categories

	High fit (~10 METs)		Moderate fit (5.1-10 METs)				Low Fit <5 METs)				p*
	W/o Diab.	With Diab.	W/o Diab.	With Diab.	W/o Diab.	With Diab.	W/o Diab.	With Diab.	W/o Diab.	With Diab.	
	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*	
Entire cohort (n=6758)											
Age Adjusted	Ref.	0.80 (0.40-1.63)	0.55	2.36 (2.04-2.74)	<0.00	2.34 (1.83-2.98)	<0.00	4.70 (4.00-5.52)	<0.00	4.58 (3.43-6.11)	<0.00
Multi adjusted	Ref.	0.85 (0.41-1.75)	0.66	2.23 (1.92-2.59)	<0.00	2.31 (1.76-3.04)	<0.00	4.07 (3.45-4.79)	<0.00	4.43 (3.24-6.06)	<0.00
Matched cohort (n=1184)											
Age Adjusted	Ref.	0.55 (0.21-1.42)	0.22	1.70 (0.95-3.04)	0.075	1.79 (0.99-3.22)	0.052	3.29 (1.77-6.12)	0<0.00	3.21 (1.72-6.02)	<0.00
Multi adjusted	Ref.	0.54 (0.21-1.38)	0.2	1.62 (0.89-2.94)	0.111	1.63 (0.89-2.98)	0.11	2.58 (1.37-4.87)	0.003	2.81 (1.49-5.31)	0.001

Figure 4. Relative risks for mortality by fitness and diabetes category, with High Fit/No Diabetes as the reference group.

RESULTS

Median follow-up was 12.14 years (IQR 8.96-16.22), providing 83,730 person-years. A total of 2091 (31%) patients died, with an average annual mortality of 24 deaths per 1000 person-years (95% CI: 23.8-25.9). Patients without Type-2 diabetes had significantly higher mortality than patients with Type-2 diabetes (1,929/6,167 vs. 162/592; 31.28% vs. 27.36% $p<0.005$). The trend in this ratio remained the same for the matched dataset (174/480 vs. 143/480; 36.25% vs. 29.79% $p<0.005$), although a small deviation from this trend was observed when comparing groups with and without diabetes with high exercise capacity. Note that this deviation was not statistically significant.

Pairs of diagnosed and undiagnosed subjects were matched using one-to-one matching without replacement on a logit of the PS using a caliper of width equal to 0.2 of the standard deviation, as this caliper has been shown to be optimal in a range of settings (11). Four hundred and eighty (81%) of the 592 patients with Type-2 diabetes were matched to patients without Type-2 diabetes with a similar propensity score. We examined balance in baseline covariates using standardized differences. Baseline balance in the 23 covariates is shown in Figure 1. Baseline characteristics of treated and untreated subjects before and after matching are reported in Table 1. As reported in Table 1 and Figure 1, after matching the pairs of treated and untreated subjects, across all baseline covariates, the differences between the two groups are reduced and also become statistically insignificant.

Clinical and exercise-test predictors of mortality from the Cox proportional hazards model are presented in Table 2 and Figure 4. Significant predictors of all-cause mortality were: age (HR 1.05, 95% CI: 1.05-1.06; $p<0.0001$), hypertension (HR

1.34, 95% CI: 1.23-1.47; $p<0.0001$), smoking (HR 1.31, 95% CI: 1.17-1.46; $p<0.0001$), Type-2 diabetes (HR 1.17, 95% CI: 0.99-1.38; $p=0.055$), body-mass index (HR 0.99, 95% CI: 0.988-0.997; $p=0.002$), and exercise capacity. For each 1 MET increase in exercise capacity, the adjusted HR for mortality was 0.87 (95% CI: 0.86-0.88; $p<0.0001$). Among clinical and exercise test variables, exercise capacity had the highest C index for predicting mortality. After adjustment for age, the C index for exercise capacity for the unmatched group, matched group with diabetes and matched group without diabetes were 0.71, 0.73, and 0.71, respectively ($p<0.001$ for all).

The effect of exercise capacity was stronger in the group with Type-2 diabetes, both for the unmatched and matched datasets. For each 1 MET increase in exercise capacity in the unmatched group, the HR for adjusted mortality was 0.83 (95% CI: 0.77-0.89; $p<0.0001$) for those with Type-2 diabetes compared to 0.87 (95% CI: 0.86-0.89; $p<0.0001$) for those without Type-2 diabetes. A similar trend was observed for the matched dataset; the adjusted HR for mortality was 0.83 (95% CI: 0.77-0.90; $p<0.0001$) for those with Type-2 diabetes compared to 0.88 for those without Type-2 diabetes (95% CI: 0.82-0.94; $p<0.0001$).

Mortality risks in both matched and unmatched groups were significantly higher for low-fit individuals with Type-2 diabetes (for matched group, HR 2.81, 95% CI: 1.49-5.31; $p<0.0001$). Interestingly, mortality risk for high-fit individuals with Type-2 diabetes was lower than that of the high-fit individuals without Type-2 diabetes (for matched group, HR 0.54, 95% CI: 0.21-1.38; $p=0.2$).

DISCUSSION

In the current study, we used a propensity score matching method to minimize the effects of confounding in estimating the degree of association between exercise capacity and mortality in male veterans with and without Type-2 diabetes. While there have been numerous studies performed on the association between health attributes and outcomes (such as between fitness and diabetes), few have considered the potential effects of unequal distribution of baseline covariates. A rarely recognized but potentially important limitation of observational studies involves the unequal distribution of covariates between comparison groups since random assignment is impossible. Propensity score analysis was employed to minimize these biases. The current sample of subjects with and without Type-2 diabetes,

an observational data set, provided an ideal opportunity to assess the influence of balancing the distributions of the covariate variables between two groups at baseline, thus potentially reducing bias on the hazard ratios. We estimated the propensity score for having Type-2 diabetes for each patient using a multivariable logistic regression model, in which the presence of Type-2 diabetes was modeled using all baseline patient characteristics in Table 1. We reported hazard ratios for both unmatched and matched datasets to compare differences in mortality.

In our study we found that the mortality risk for high-fit individuals with Type-2 diabetes was lower than that of the high-fit individuals without Type-2 diabetes (Figs 2 and 3). Our observation supports previous findings for an inverse relationship between exercise and all-cause mortality in both healthy and diseased populations (13-16). Our study is first of its kind to provide comparative information on the association between exercise capacity and all cause mortality risk in veteran populations with or without Type 2-diabetes by using propensity matching. Therefore, it is worth emphasizing a strong inverse reduction in mortality risk for fit individuals and diabetes. For example, the adjusted mortality risk reduction per each 1-MET increase in exercise capacity for unmatched group was 0.83 for those with Type-2 diabetes compared to 0.87 for those without Type-2 diabetes. Similarly for matched group it was 0.83 for those with Type-2 diabetes compared to 0.88 for those without Type-2 diabetes. Furthermore, in this particular study comparisons between six fitness-diabetes categories revealed significant and clinically relevant differences in the mortality risk reduction between healthy and diseased veterans.

In this study, although the trend in the association between exercise capacity and all-cause-mortality remained similar for both matched and unmatched data, the hazard ratios for the unmatched data were relatively inflated. This was particularly true for the lower fit groups, in which mortality was inflated by roughly 40% regardless of the presence of Type-2 diabetes (Fig. 4). Such differences suggest that, without minimizing the impact of confounding variables, results derived from an unmatched dataset may be influenced by the presence of bias due to confounding.

The possible causative mechanism(s) behind the association of exercise capacity and mortality risk in diabetic veteran are not readily evident and are beyond the scope of this study. Nevertheless, vascular reactivity may have been more prevalent in the context

of the current study and may be considered as one of the important factor. Moreover, veterans avail high standard health care facilities and they have access to these facilities for a longer period of time which may provide protection against premature mortality even if they are diabetic.

The current findings confirm recent studies on the important role of fitness in determining health outcomes in diabetics (12-14). Our findings are consistent with the concept that even small improvements in fitness have a significant impact on health outcomes. The reduction in mortality per MET achieved both with and without propensity matching is consistent with the 10-20% benefit per MET in patients with cardiovascular disease and other conditions (15). Because physical activity is a key factor for the development of fitness, physical activity interventions will positively impact health among Type-2 diabetics. Favorable effects of physical activity in Type-2 diabetes include improved insulin resistance and glucose control, along with positive effects on blood lipids, blood pressure, and weight control (16). Physical activity programs are imperative in light of the increase in prevalence in diabetes over the last two decades and given the estimated 300 million individuals worldwide that will be affected by this condition by 2025 (17). Undoubtedly, the success of exercise campaigns will require significant education and innovation as the majority of persons with Type-2 diabetes maintain sedentary lifestyles (18, 19). Future advocacy and research efforts aiming to increase fitness status in the Type-2 diabetes population should consider factors that include personal motivation, health and mobility management, genetic predisposition, and environmental modification of the physical and social environment (20).

Limitations

Our sample consisted of men only, which reflects the fact that roughly 96% of subjects referred to our Veterans Affairs exercise laboratory are men. Thus, the results may not be applicable to women. In addition, the current results are based on clinical, demographic, and exercise test data from a baseline visit and the association of these data with all-cause mortality; we do not have data on other subsequent health problems or cause of death.

In conclusion, using a propensity matching method to reduce baseline bias, exercise capacity was found to be a strong predictor of mortality in veterans with and without Type-2 diabetes. Although the trend in

the association between exercise capacity and all-cause-mortality was similar for matched and unmatched data, the mortality risks were relatively inflated when using unmatched data. Such differences suggest that, without minimizing the impact of confounding variables, results derived from an unmatched dataset may be biased. This has potential implications for related studies on the association between health risks and outcomes. While the overall effect of this statistical approach was modest, the current findings nonetheless provide further support for efforts to improve fitness through physical activity among individuals with diabetes. Physical activity counseling should be included as a standard part of clinical encounters in patients with diabetes.

Conflict of interest

The authors declare that they have no conflict of interest.

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