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Prognostic value of exercise capacity in incident diabetes: a country with high prevalence of diabetes

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Abstract

Background Diabetes Mellitus (DM) is a fast-growing health problem that imposes an enormous economic burden. Several studies demonstrated the association between physical inactivity and predicting the incidence of diabetes. However, these prediction models have limited validation locally. Therefore, we aim to explore the predictive value of exercise capacity in the incidence of diabetes within a high diabetes prevalence population.

Methodology A retrospective cohort study including consecutive patients free of diabetes who underwent clinically indicated treadmill stress testing. Diabetic patients at baseline or patients younger than 18 years of age were excluded. Incident diabetes was defined as an established clinical diagnosis post-exercise testing date. The predictive value of exercise capacity was examined using Harrell's c-index, net reclassification index (NRI), and integrated discrimination index (IDI).

Results A total of 8,722 participants (mean age 46 ± 12 years, 66.3% were men) were free of diabetes at baseline. Over a median follow-up period of 5.24 (2.17–8.78) years, there were 2,280 ($\approx 26\%$) new cases of diabetes. In a multivariate model adjusted for conventional risk factors, we found a 12% reduction in the risk of incident diabetes for each METs achieved (HR, 0.9; 95% CI, 0.88–0.92; $P < 0.001$). Using Cox regression, exercise capacity improved the prediction ability beyond the conventional risk factors (AUC = 0.62 to 0.66 and c-index = 0.62 to 0.68).

Conclusion Exercise capacity improved the overall predictability of diabetes. Patients with reduced exercise capacity are at high risk for developing incidence diabetes. Improvement of both physical activity and functional capacity represents a preventive measure for the general population.

Keywords Incident Diabetes, Exercise Capacity, Metabolic equivalent of tasks (METs), Net reclassification index, Predictive modeling

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Background

Diabetes is a major socio-economic health problem, with prevalence expanding globally over the past decades[1] making diabetes prevention a crucial health priority[2, 3]. Strong evidence engaging higher levels of exercise capacity and lifestyle interventions has shown a protective impact on subsequent diabetes[3, 4]. Physical activity influences cardiorespiratory fitness (CRF), which reflects the well-being of the cardiovascular system and muscular strength[5]. The significance of this evidence has led several organizations, including the American Heart Association, the American Diabetes Association, and the US Department of Health and Human Services to include exercise capacity in their recommendations and guidelines[6, 7]. However, it remains controversial how other diabetes-related risk factors, especially metabolic syndrome elements, might alter the association between fitness and incident diabetes.

The actual effect of exercise capacity on diabetes has not been fully explored as most previous data exemplify nations with low to intermediate disease prevalence[8, 9]. These data reflect societies where the culture of exercise is dominant; however, in the Middle East and North Africa (MENA), a rise in prevalence is likely to occur considering low activity levels among citizens.

We are aiming to extend the exploration of the predictive value of exercise capacity in incidence diabetes by (1) examining the relationship between exercise capacity and incident diabetes among patients free of diabetes at baseline and (2) examining whether the relationship between CRF and incident diabetes differed across demographic characteristics and other traditional diabetes-related risk factors. Furthermore, we assess the relationship between Duke Treadmill Score, exercise capacity, and incidence of diabetes.

Methods

Study design and population

A retrospective cohort study included patients who underwent clinically indicated exercise treadmill stress testing at King Abdulaziz cardiac center between April 2001 and December 2016. King Abdulaziz Cardiac Center is a part of a large well-connected health care system providing medical service through primary health care up to the tertiary level which makes patients tracking accessible [10]. The patient's demographics, medical history, and medications used before the stress test were obtained by reviewing the electronic medical record and database search using the ICD-9 coding system. The exercise stress testing system (MUSE) was used to extract exercise test results. Diabetes at the baseline, young patients (<18 years), records with incomplete stress testing information, and non-Bruce protocol exercise stress testing were excluded from the study analysis. The study

was conducted in full accordance with the protocol and the current revision of the declaration of Helsinki, the Good Clinical Practice. The study was a part of the Saudi CardioRespiratory Fitness (SCARF) project (Study protocol: RC16/103/R - approved by King Abdullah International Medical Research Center (KAIMRC)).

Exercise treadmill stress testing

Patients underwent symptom-limited maximal treadmill stress testing, which followed the standard Bruce protocol. The test day was pointed as the individual study baseline. Individual results of the initial exercise test were included in the database. Resting both heart rate and blood pressure were measured in the seated position and recorded immediately before each test. Supervised clinicians were following American Heart Association/American College of Cardiology (AHA/ACC) guidelines for terminating the test if the patient had Exercise limiting symptoms: chest pain, shortness of breath, significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, other limiting symptoms independent of the achieved heart rate or if the participant was unwilling or unable to continue. Otherwise, patients could reach their peak attainable workload independent of the heart rate achieved. Target heart rate was calculated as 85% of the age-predicted maximal heart rate; the patient's age was subtracted from a constant value of 220. Metabolic equivalents (METs) were adopted to represent cardiorespiratory fitness status based on the workload derived from the maximal speed and grade achieved during the total treadmill time. METs results were categorized into four groups: <6, 6–9, 10–11, and ≥ 12 METs.

Study definitions for risk factors

The history of hypertension was defined as a prior diagnosis of hypertension or the use of antihypertensive medications at the time of stress testing. Dyslipidemia was defined as the prior diagnosis of any significant lipid abnormality in the medical records or lipid-lowering medication use. On a prior angiogram, patients with obstructive coronary artery disease (CAD), prior myocardial infarction, coronary angioplasty, or coronary artery bypass surgery are considered known coronary artery disease. Prior congestive heart failure was defined as a prior clinical diagnosis of systolic or diastolic heart failure.

Study outcome: Incident Diabetes

Incident diabetes was determined among patients without diabetes at baseline and defined as clinical diagnosis of diabetes in the medical records or clinical problem list, use of anti-hyperglycemic medications including

insulin, or had lab results suggestive of diabetes post-exercise testing date without further details on the type of diabetes. Time-to-incident diabetes was based on the time between treadmill testing and the date of the first encounter with a new diabetes diagnosis.

Statistical analysis plan

Study participants were divided into four groups based on their METs (<6, 6–9, 10–11, and ≥ 12). Categorical variables were presented in frequencies and percentages. Continuous variables were presented based on the normality of distribution as mean \pm standard deviation or median and interquartile ranges, as appropriate. The four groups were compared using Chi-square or Fisher exact test for categorical variables. Analysis of Variance (ANOVA) and Kruskal Wallis test was used for continuous variables comparison, as appropriate. Cumulative incidence was presented at 5-, 10-, and 15-yr intervals via a bar graph.

Kaplan-Meier cumulative incident diabetes was computed for different exercise capacity groups, and they were compared using the log-rank test. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI). A forward selection technique was used to demonstrate independent predictors of incident diabetes. In each forward step, we added a related set of variables to improve our model. Gender, age, and heart rate were included in the baseline model (model 1). Subsequently, cardiovascular risk factors (model 2), Medications used (model 3), and exercise stress testing findings (model 4). We computed Harrell's concordance index (C-index) area under the Curve (AUC) and Akaike information criterion (AIC) to compare the models using this methodology developed for the incidence of diabetes. The selection of variables for entry consideration was based on clinical judgment, results of previous publications, and the expertise of the investigators. We also plotted a restricted cubic spline model to show the shape of the continuous relationship between METs and incident diabetes after adjustment for covariates. Finally, we examined the association between METs and incident diabetes in the subset of participants with a BMI measurement ($N=6,539$) (Supplementary Table 1). All Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $P \leq 0.05$.

Results

Our study included 8,722 participants without diabetes at baseline. The mean age of study participants was 46 ± 12 years, and 66.5% were men; 33.9% were hypertensive; 28.3% had hyperlipidemia; 5.4% were known to have prior coronary artery disease (CAD), and only a few of them had heart failure (Table 1).

Participants with the highest exercise capacity (≥ 12 METs) were younger (41 ± 3 vs. 51 ± 12 years, $p < 0.001$); more often males (91% versus 43%, $p < 0.001$); had lower mean body mass index (26 ± 9 vs. 32 ± 3 kg/m², $p < 0.001$) and less likely to have hypertension or hyperlipidemia (26% vs. 44% and 25% vs. 29%, respectively, $p < 0.001$) in comparison with the lowest exercise capacity group (METs < 6). No apparent differences between CRF categories regarding prior coronary artery disease (CAD) and heart failure were observed. At peak exercise, the heart rate was higher among the highest achievers (166 ± 2 vs. 131 ± 25 bpm, $p < 0.001$) as well as systolic blood pressure (161 ± 21 vs. 153 ± 33 mmHg, $p < 0.001$). Moreover, the highest METs-achieved was associated with a lower risk of Duke Treadmill risk, while high Duke Treadmill risk was observed in those with lower METs achieved (for low Duke score: 77.2% vs. 19.4%) and (for high Duke score 0.7% vs. 2.7%), $p < 0.001$.

Over a median follow-up period of 5.24 (IQR: 2.17–8.78) years, there were 2,280 (25.96%) new cases of diabetes. The unadjusted 5-year accumulative incidence rates of diabetes across categories of CRF (<6, 6<9, 10<11, and ≥ 12 METs) were 25.1%, 16.9%, 9.4%, and 6.2%, respectively. The cumulative rates of incidence of diabetes by the end of 15 year follow-up period were as follows: 40.6%, 31.9%, 23.2%, and 17.3% for those who achieved <6, 6<9, 10<11, and ≥ 12 METs, respectively (Fig. 1).

Examination of the crude association between categories of METs and risk for incident diabetes using a Kaplan-Meier cumulative incidence curve revealed a significant trend across categories of METs (log-rank < 0.001) (Fig. 2). In a multivariate Cox regression model adjusted for potential confounders, we found a 10% reduction in the risk of incident diabetes with higher METs achieved (HR, 0.90; 95% CI, 0.88–0.92; $p < 0.001$) (model 4B) and risk for incident diabetes reduced per each METs achieved; 13% (6<9 METs), 38% (10<11), and 52% (≥ 12 METs) compare to lower METs (<6 METs) $p < 0.001$. Adding the exercise capacity information (METs achieved, CI, and Duke Risk score) improves the overall predictability of the model (model 4 A) over the baseline model (Table 2A). Examining the predictive value of the finding of exercise stress testing (using AIC, C-statistics, IAUC, NRI, and IDI), we found superiority of METs groups in the prediction incidence of diabetes above the other models resulting in a significant reclassification of the study cohort and significant improvement of the area under the curve above the primary model (Table 2B).

A non-linear inverse relationship was observed between baseline exercise capacity and risk of incident diabetes after adjusting for known confounders. A

Table 1 Baseline characteristics of the study cohort

	Total	METs < 6	METs 6–9	METs 10–11	METs ≥ 12	p-value
	8722	589 (6.7%)	3077 (35.3%)	2930 (33.6%)	2126 (24.4%)	
Age (year)	45.9 ± 12.06	50.9 ± 12.37	48.4 ± 11.87	45.5 ± 11.81	41.3 ± 10.96	< 0.0001
Gender (Male)	5798 (66.5%)	254 (43.1%)	1410 (45.8%)	2157 (73.6%)	1977 (93.0%)	< 0.0001
Height (cm)	162.2 ± 19.51	157.8 ± 18.52	159.4 ± 17.97	164.2 ± 17.85	165.0 ± 23.49	< 0.0001
Weight (kg)	79.7 ± 16.55	81.7 ± 18.08	81.3 ± 17.51	79.5 ± 16.52	77.2 ± 14.11	< 0.0001
BMI (kg/m ²)	29.4 ± 6.15	32.3 ± 7.22	31.2 ± 6.58	28.5 ± 5.23	26.9 ± 5.10	< 0.0001
Cardiovascular risk factors						
Hypertension	2955 (33.9%)	258 (43.8%)	1154 (37.5%)	987 (33.7%)	556 (26.2%)	< 0.0001
Hyperlipidaemia	2465 (28.3%)	172 (29.2%)	880 (28.6%)	884 (30.2%)	529 (24.9%)	0.0005
Known CAD	474 (5.4%)	27 (4.6%)	157 (5.1%)	184 (6.3%)	106 (5.0%)	0.0938
Known CHF	66 (0.8%)	4 (0.7%)	30 (1.0%)	23 (0.8%)	9 (0.4%)	0.1593
Prior CABG	131 (1.5%)	10 (1.7%)	57 (1.9%)	43 (1.5%)	21 (1.0%)	0.0885
Prior MI	454 (5.2%)	30 (5.1%)	151 (4.9%)	172 (5.9%)	101 (4.8%)	0.2524
Prior PCI	306 (3.5%)	16 (2.7%)	92 (3.0%)	123 (4.2%)	75 (3.5%)	0.0538
Smoking	277 (3.2%)	34 (5.8%)	88 (2.9%)	107 (3.7%)	48 (2.3%)	< 0.0001
Lung disease	348 (4.0%)	37 (6.3%)	145 (4.7%)	124 (4.2%)	42 (2.0%)	< 0.0001
Lab results*						
Cholesterol	4.6 (3.87, 5.30)	4.4 (3.80, 5.20)	4.5 (3.84, 5.28)	4.5 (3.87, 5.33)	4.6 (3.95, 5.35)	0.0142
Triglyceride	1.4 (0.99, 1.86)	1.4 (1.04, 1.94)	1.3 (0.98, 1.82)	1.4 (0.98, 1.89)	1.4 (1.02, 1.91)	0.0128
HDL	1.0 (0.88, 1.22)	1.0 (0.87, 1.22)	1.1 (0.90, 1.25)	1.0 (0.87, 1.22)	1.0 (0.88, 1.18)	< 0.0001
LDL	2.8 (2.22, 3.49)	2.7 (2.10, 3.32)	2.8 (2.19, 3.43)	2.8 (2.22, 3.51)	2.9 (2.29, 3.62)	< 0.0001
Haemoglobin	143 (129, 154)	133.0 (121, 144)	136.0 (123, 148)	146.0 (132, 156)	152.0 (142, 160)	< 0.0001
Haematocrit	0.4 (0.39, 0.46)	0.4 (0.37, 0.43)	0.4 (0.37, 0.44)	0.4 (0.40, 0.46)	0.4 (0.42, 0.47)	< 0.0001
Calcium	2.3 (2.25, 2.40)	2.3 (2.20, 2.35)	2.3 (2.23, 2.39)	2.3 (2.25, 2.39)	2.4 (2.28, 2.42)	< 0.0001
BUN	4.6 (3.80, 5.80)	4.5 (3.60, 6.00)	4.5 (3.60, 5.80)	4.7 (3.80, 5.80)	4.8 (4.00, 5.80)	< 0.0001
Creatinine	75.0 (64.00, 89.00)	69.5 (60.00, 85.00)	70.0 (60.00, 84.00)	75.0 (65.00, 88.00)	81.0 (72.00, 93.00)	< 0.0001
eGFR	94.7 (80.39, 109.42)	92.8 (77.29, 106.46)	93.7 (78.85, 107.83)	95.8 (81.84, 110.79)	94.3 (81.44, 110.09)	0.0001
hsCRP	2.5 (0.93, 5.00)	6.0 (2.78, 11.00)	3.5 (1.24, 6.16)	2.7 (0.85, 5.00)	1.4 (0.78, 2.38)	0.0001
Vitamin-D	32.9 (23.00, 48.00)	29.8 (21.00, 47.00)	33.0 (22.20, 49.00)	33.3 (23.15, 49.40)	32.6 (23.90, 46.00)	0.0001
Medications						
Beta-blockers	710 (8.1%)	61 (10.4%)	268 (8.7%)	247 (8.4%)	134 (6.3%)	0.0017
Calcium channel blockers	503 (5.8%)	54 (9.2%)	202 (6.6%)	159 (5.4%)	88 (4.1%)	< 0.0001
ACEI	512 (5.9%)	40 (6.8%)	177 (5.8%)	191 (6.5%)	104 (4.9%)	0.0753
ARB	988 (11.3%)	86 (14.6%)	386 (12.5%)	341 (11.6%)	175 (8.2%)	< 0.0001
ACEARB	1288 (14.8%)	107 (18.2%)	489 (15.9%)	452 (15.4%)	240 (11.3%)	< 0.0001
Aspirin	875 (10.0%)	60 (10.2%)	309 (10.0%)	328 (11.2%)	178 (8.4%)	0.0123
Digoxin	48 (0.6%)	7 (1.2%)	20 (0.6%)	12 (0.4%)	9 (0.4%)	0.0847
PPI	744 (8.5%)	59 (10.0%)	271 (8.8%)	284 (9.7%)	130 (6.1%)	< 0.0001
Plavix	2057 (23.6%)	149 (25.3%)	718 (23.3%)	717 (24.5%)	473 (22.2%)	0.2169
Statin	1388 (15.9%)	86 (14.6%)	483 (15.7%)	506 (17.3%)	313 (14.7%)	0.0674
Diuretic	357 (4.1%)	41 (7.0%)	154 (5.0%)	110 (3.8%)	52 (2.4%)	< 0.0001
Stress test results						
Rest HR (bpm)	81.9 ± 16.12	86.9 ± 18.45	84.8 ± 17.00	81.1 ± 15.05	77.5 ± 14.21	< 0.0001
Peak HR (bpm)	155.5 ± 22.13	130.9 ± 25.28	149.8 ± 21.76	158.5 ± 18.79	166.7 ± 17.53	< 0.0001
Rest SBP (mmHg)	129.8 ± 16.94	133.0 ± 19.06	130.7 ± 18.34	129.1 ± 16.04	128.4 ± 14.98	< 0.0001
Peak SBP (mmHg)	160.8 ± 25.92	152.7 ± 32.48	160.7 ± 28.64	162.4 ± 24.55	160.7 ± 21.29	< 0.0001
Rest DBP (mmHg)	79.2 ± 9.88	79.5 ± 10.07	78.6 ± 10.38	79.6 ± 9.45	79.5 ± 9.62	0.0034
Peak DBP (mmHg)	82.8 ± 10.63	82.3 ± 10.89	83.4 ± 10.77	83.4 ± 10.76	81.2 ± 10.06	< 0.0001
Peak METs	10.1 ± 2.80	4.7 ± 0.95	8.0 ± 1.04	10.7 ± 0.62	13.6 ± 1.48	< 0.0001
Chronotropic Incompetence	2275 (26.1%)	391 (66.4%)	1013 (32.9%)	591 (20.2%)	280 (13.2%)	< 0.0001
Duke Treadmill Score	5.5 ± 6.12	1.8 ± 5.79	4.0 ± 5.43	6.2 ± 5.73	7.9 ± 6.56	< 0.0001

(continued) Table 1

	Total	METs < 6	METs 6–9	METs 10–11	METs ≥ 12	p-value
	8722	589 (6.7%)	3077 (35.3%)	2930 (33.6%)	2126 (24.4%)	
Low	6040 (69.3%)	114 (19.4%)	2064 (67.1%)	2221 (75.8%)	1641 (77.2%)	< 0.0001
Moderate	2447 (28.1%)	454 (77.1%)	925 (30.1%)	597 (20.4%)	471 (22.2%)	
High	235 (2.7%)	21 (3.6%)	88 (2.9%)	112 (3.8%)	14 (0.7%)	

CAD: Coronary artery disease, CHF: Congestive heart failure, CABG: Coronary artery bypass grafting, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, HDL: High density lipoprotein, LDL: Low density lipoprotein, BUN: Blood urea nitrogen, eGFR: estimated Glomerular filtration rate, ACEI: Angiotensin converting enzyme inhibitors, ARB: Angiotensin Receptor blocker, PPI: Proton pump inhibitors, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, METs: Metabolic equivalent of tasks

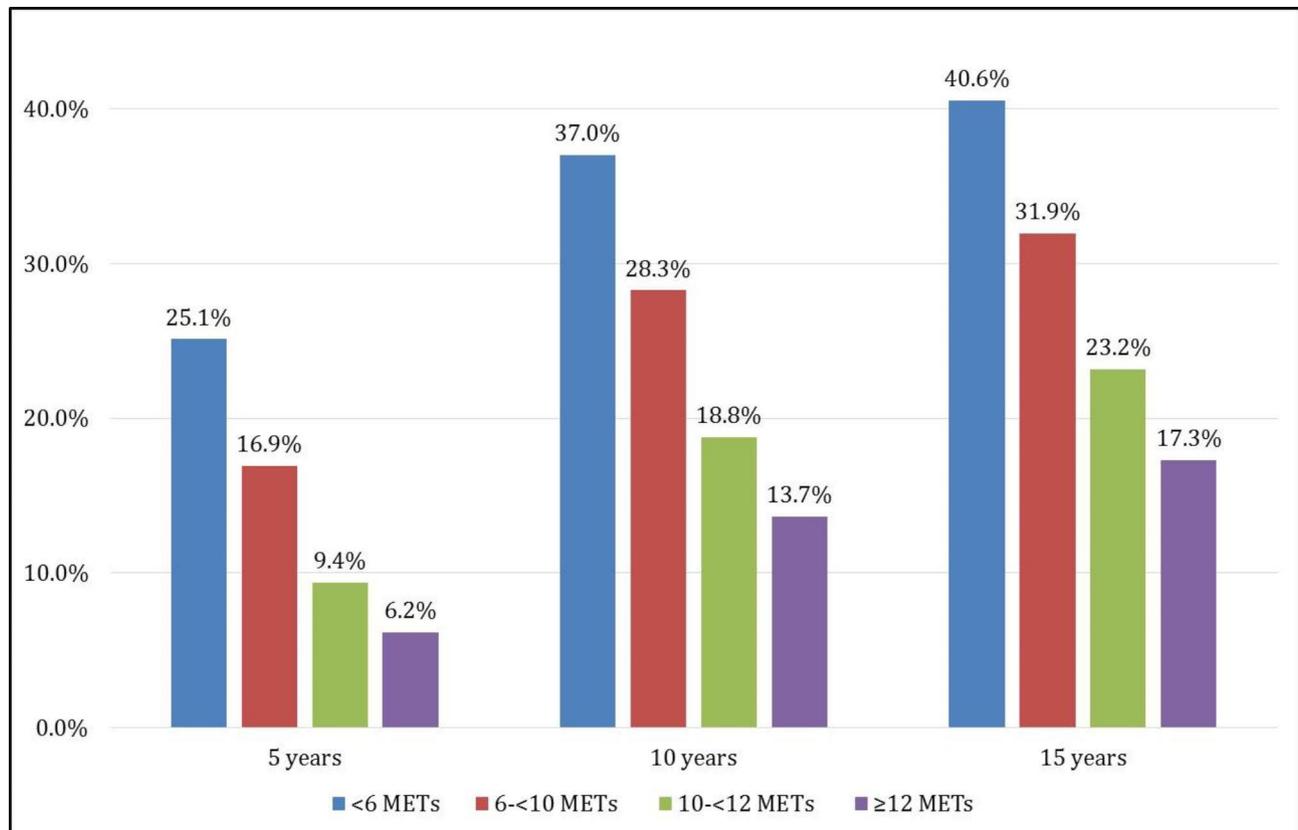


Fig. 1 The cumulative rates of incidence diabetes

gradual decline in the risk of development of diabetes was observed for every improvement of exercise capacity (METs increase) above 6 METs (Fig. 3).

Discussion

This study investigated the relationship between exercise capacity and incident diabetes. To the best of our knowledge, it is the first large and demographically diverse cohort to examine the association between CRF estimated by METs using a standard test (Bruce protocol) by exercise treadmill testing and the risk of incident diabetes in the MENA region. It has shown that higher fitness was inversely associated with incident diabetes, such that every increment of fitness by 1 METs was associated with a 12% lower risk of incident diabetes. Another important finding in our study was

the inverse linear relationship between CRF and diabetes, which notably did not show evidence of plateauing or reversal at higher levels of CRF regardless of age, sex, or other diabetes risk factors.

The mechanism that links the relationship between fitness and incident diabetes is a subject of much discussion. Individuals with low cardiorespiratory fitness have high insulin resistance[11], and low levels of CRF have fewer glucose transporters[12] compared with those more fit. It is thought to be mediated by positive changes in the human body tissue profile, reduced adiposity[13], and an immediate increase in insulin sensitivity and glucose disposal[14]. However, several studies have shown that impaired oxidative respiration due to mitochondrial dysfunction[15] underlies

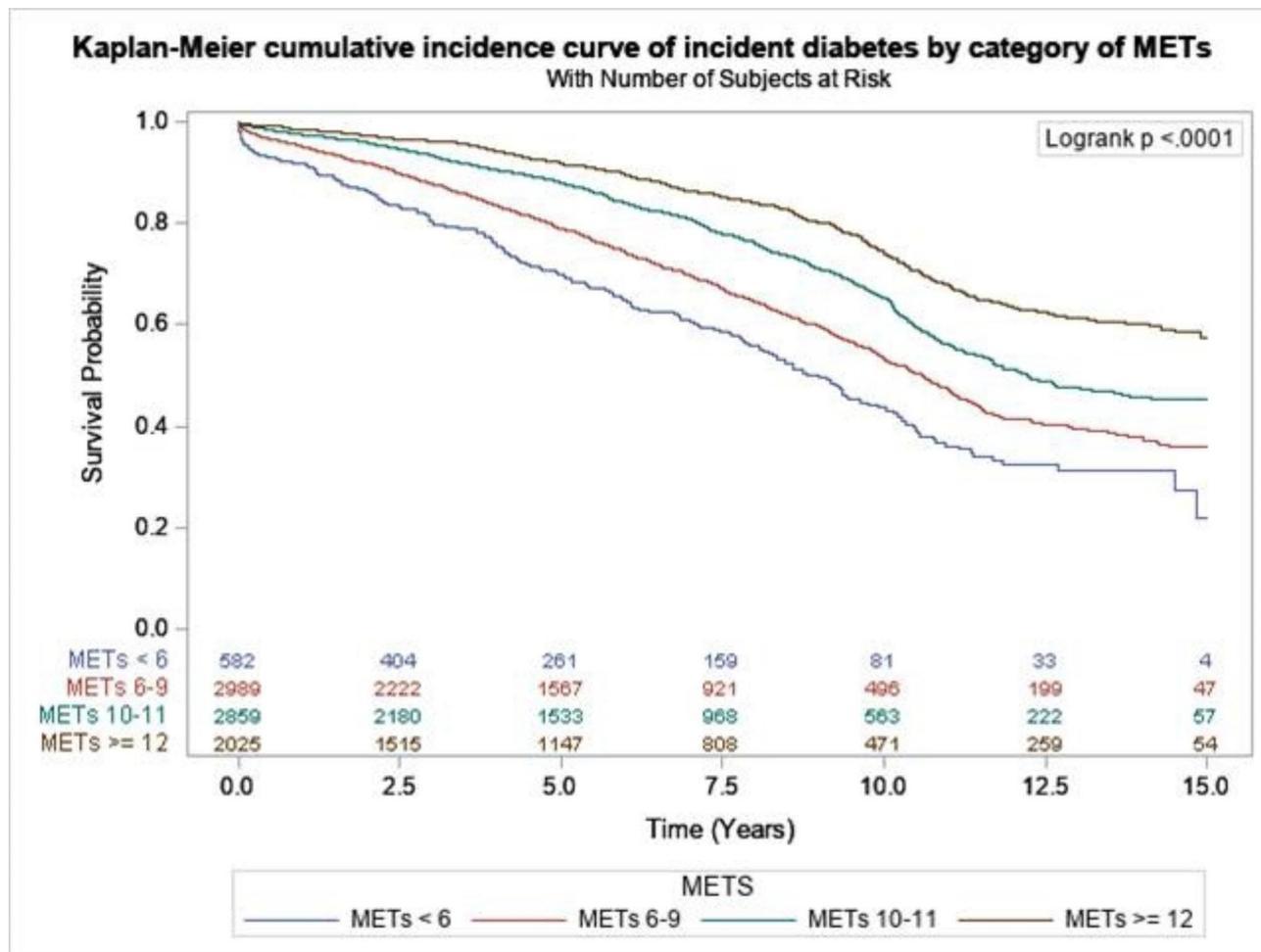


Fig. 2 Kaplan-Meier cumulative incidence curve and the trends across categories of METs

the pathogenesis of diabetes reflecting a native genetic state independent of physical activity[16].

Scattered small cross-sectional studies have shown that exercise capacity is inversely associated with impaired glycemic control[17], the metabolic syndrome[18], diabetes[19] and positively associated with glucose disposal rate and insulin sensitivity[20]. Unfortunately, these studies have been small and confined to limited demographic settings (single-sex, racial group, or age-group). Others had reported the relationship between CRF level and the incident diabetes in prospective[21–23] or measuring CRF differently[24].

Low CFR in diabetic patients is an independent risk factor for mortality, and it was associated with 2.1 odds of mortality compared with high CFR diabetic patients[25]. Long-standing diabetes leads to consequences of peripheral neuropathy and vasculopathy with the reduction in the activity of daily living, poor physical function, and disability[26–28]. Additionally, concomitant diabetes risk factors expedite the complications’ progression and highlight the need for urgent intervention on several

prevention levels[29]. Implementing the WHO recommendations for reducing physical inactivity by 10–15% will gradually reduce T2DM in adults[30]. A 150-min of moderate-intensity exercise weekly was associated with a reduction of T2DM by 26%[31].

Study limitations and strengths

Our study is not without limitations. First, cardiovascular health is independently associated with behaviors that may represent the causal contributing to fitness. Unfortunately, we are unable to assess these behaviors in our study formally. Second, incident diabetes was based on medical records and administrative claims files, which were not collected initially to examine diabetes. As a result, our study did not include study protocol-based direct measurements of hemoglobin A1c, blood glucose, or oral glucose tolerance testing. Because of this, several people with undiagnosed diabetes may have been included in our study population or missed as incident cases, attenuating our results. Third, our study population comprised persons

Table 2A Adjusted multivariate Cox regression model for exercise stress testing

	Model (1)		Model (2)		Model (3)		Model (4 A)		Model (4B)	
	HR (95% CI)	p								
Age (years)	1.032 (1.03–1.04)	<0.001	1.028 (1.02–1.03)	<0.001	1.028 (1.02–1.03)	<0.001	1.022 (1.02–1.03)	<0.001	1.02 (1.02–1.02)	<0.001
Gender (Female vs. Male)	1.131 (1.03–1.24)	0.009	1.176 (1.07–1.29)	0.001	1.138 (1.04–1.25)	0.007	0.892 (0.81–0.99)	0.027	0.87 (0.79–0.96)	0.007
Resting heart rate (bpm)	1.002 (1.00–1.00)	0.109	1.003 (1.00–1.01)	0.011	1.004 (1.00–1.01)	0.003	1.002 (1.00–1.01)	0.109	1.001 (1.00–1.00)	0.452
Cardiovascular risk factors										
Hypertension			1.189 (1.08–1.31)	<0.001	1.138 (1.03–1.26)	0.015	1.06 (0.95–1.18)	0.284	1.059 (0.95–1.18)	0.293
Hyperlipidemia			1.196 (1.08–1.32)	<0.001	1.502 (1.36–1.66)	<0.001	1.537 (1.39–1.70)	<0.001	1.539 (1.39–1.71)	<0.001
Smoking			1.202 (0.94–1.54)	0.150	1.241 (0.97–1.59)	0.090	1.19 (0.93–1.52)	0.167	1.178 (0.92–1.51)	0.193
Lung disease			1.06 (0.77–1.46)	0.720	0.961 (0.69–1.34)	0.814	0.94 (0.67–1.31)	0.716	0.908 (0.65–1.27)	0.572
Known CAD			1.154 (0.98–1.36)	0.092	1.149 (0.97–1.37)	0.117	1.18 (0.99–1.40)	0.060	1.189 (1.00–1.41)	0.049
Known CHF			0.588 (0.36–0.97)	0.039	0.483 (0.29–0.81)	0.005	0.431 (0.26–0.72)	0.001	0.429 (0.26–0.71)	0.001
Medications										
Statins					0.332 (0.28–0.40)	<0.001	0.338 (0.28–0.41)	<0.001	0.338 (0.28–0.41)	<0.001
PPI					1.632 (1.32–2.01)	<0.001	1.563 (1.27–1.93)	<0.001	1.568 (1.27–1.94)	<0.001
CCB					0.994 (0.81–1.21)	0.955	1.005 (0.82–1.23)	0.964	0.999 (0.82–1.22)	0.993
BB					1.697 (1.38–2.09)	<0.001	1.615 (1.31–1.99)	<0.001	1.588 (1.29–1.96)	<0.001
ACE/ARB					0.996 (0.86–1.15)	0.951	0.979 (0.85–1.13)	0.771	0.988 (0.86–1.14)	0.866
Diuretic					1.187 (0.95–1.48)	0.124	1.182 (0.95–1.47)	0.138	1.164 (0.93–1.45)	0.178
METs (Categories)										
METs 6–9							0.871 (0.75–1.01)	0.073		
METs 10–11							0.619 (0.52–0.73)	<0.001		
METs ≥ 12							0.482 (0.39–0.59)	<0.001		
METs (Continuous)									0.90 (0.88–0.92)	<0.001
Chronotropic incompetence							1.119 (1.01–1.24)	0.030	1.056 (0.95–1.17)	0.303
Duke Risk Score										
High Risk							1.293 (1.00–1.67)	0.048	1.257 (0.97–1.62)	0.078
Moderate Risk							1.26 (1.14–1.39)	<0.001	1.21 (1.10–1.33)	<0.001

h: Hazard ratio, **CI:** confidence interval, **CAD:** Coronary artery disease, **CHF:** Congestive heart failure, **PPI:** Proton pump inhibitors, **CCB:** Calcium channel blocker, **BB:** beta-blockers, **ACE/ARB:** Angiotensin-converting enzyme/Angiotensin receptor blockers, **METs:** Metabolic equivalent of tasks,

referred for stress testing, which undoubtedly carries a higher burden of cardiovascular disease at baseline than the general population and may have led to referral bias. That limits our study’s generalizability. Fourth,

residual confounding is always a concern with observational studies, especially with covariates assessed via the medical record rather than a direct measurement. Finally, our study reports a single center’s experience

Table 2B Predictive value of the models finding for exercise stress testing

	Model (1)	Model (2)	Model (3)	Model (4 A)	Model (4B)
AIC	36619.287	36573.79	36408.081	36253.129	36227.135
C-Statistics	0.6221	0.6289	0.6581	0.6817	0.6839
IAUC	0.6256	0.6352	0.6581	0.6911	0.6948
NRI	0.3757	0.2451	0.3562	0.1595	0.129
IDI	0.0123	0.0019	0.0065	0.0026	0.0026

Model [1]: Age, Gender, Resting heart rate.

Model [2]: Model [1]+ Cardiovascular risk factors.

Model (3): Model (2) + Medications used.

Model (4A): Model (3) + Finding of exercise stress testing (METs in categories)

Model (4B): Model (3) + Finding of exercise stress testing (METs as continuous)

AIC: Akaike information criterion, **C-statistics:** concordance statistic, **IAUC:** Incremental Area Under the Curve, **NRI:** Net reclassification improvement, **IDI:** Integrated Discrimination Index

with its unique practice patterns and mode of operation. Thus, although the cohort studied was diverse, it may not represent the entire adult population of Saudi Arabia.

On the other hand, our study has some strengths. The standard stress testing, the Bruce protocol treadmill test, characterized fitness rather than self-reporting physical activity. This way is readily interpreted in clinical settings. Furthermore, our study sample was a large and diverse sample, which adequately powered our study.

Conclusion

In conclusion, our results showed a strong inverse relationship between cardiorespiratory fitness and the development of type 2 diabetes. This relationship was independent of other traditional risk factors for diabetes. This study provides further supporting evidence of the benefits of higher overall fitness. Maintaining a high cardiorespiratory fitness level may contribute to the prevention of type 2 diabetes; therefore, we hope our findings will encourage health professionals to advise the general public and diabetics to lead an active lifestyle and improve their fitness levels. Prospective future studies are required to evaluate these findings further.

Association Between Post Diabetes Mellitus and METs

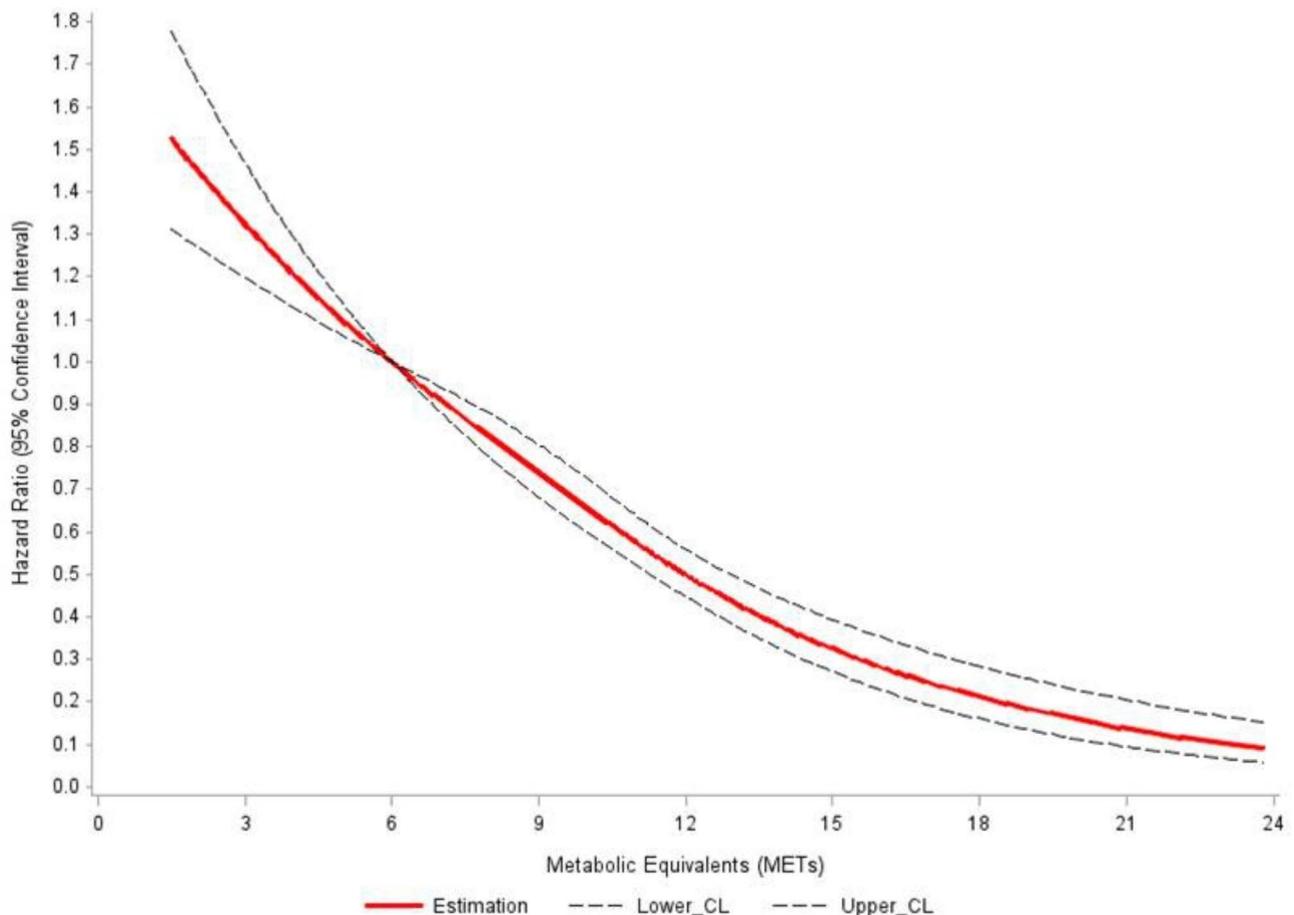


Fig. 3 The relationship of incidence diabetes risk observed for every improvement of exercise capacity

Abbreviations

DM	Diabetes mellitus
CRF	Cardiorespiratory fitness
MENA	Middle East and North Africa
ICD	International Classification of Diseases
SCARF project	Saudi CArdioRespiratory Fitness project
KAIMRC	King Abdulla International Medical Research Center
AHA/ACC	American Heart Association/American College of Cardiology
METS	Metabolic equivalents of tasks
CAD	Coronary artery disease
ANOVA	Analysis of Variance
HR	Hazard ratios
CI	confidence intervals
AIC	Akaike information criterion
AUC	Area under the Curve
C-index	Concordance index
IDI	Integrated discrimination index
AIC	Akaike information criterion
C-statistics	concordance statistic
IAUC	Incremental Area Under the Curve
NRI	Net reclassification improvement
IDI	Integrated Discrimination Index

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12902-022-01174-5>.

Supplementary Material 1

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None.

Authors' contributions

All authors (AJ, HA, AA, and MA) contributed equally to all stages of the study and agree on the final version of the manuscript.

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Data availability

The datasets generated are not for publicly sharing according to the policy declared by King Abdullah International Medical Research Center in Riyadh-Saudi Arabia and a data sharing agreement has to be signed for that with King Abdullah International Medical Research Center through the corresponding author on reasonable request.

Declarations

Ethics approval and informed consent to participate

The study protocol and waved consent were approved by ethical committee of King Abdullah International Medical Research Center. Study protocol number: RC16/103/R.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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