7-24-2021

Differential Age-Related Declines in Cardiorespiratory Fitness Between People With and Without Type 2 Diabetes Mellitus

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Abstract

Objective: To assess the extent to which the established age-related decline in cardiorespiratory fitness (CRF) is augmented in adult men with type 2 diabetes mellitus (T2DM).

Participants and Methods: This study used data from the Aerobics Center Longitudinal Study, conducted between September 18, 1974, and August 3, 2006, in primarily non-Hispanic white, middle-to-upper class adults. The analyses were restricted to adult men with complete data on age, CRF, and T2DM (35,307 participants). Quantile regression models were used to estimate age-related differences in CRF, estimated using a maximal treadmill test, between persons with and without T2DM. Smoking status and birth cohort served as covariates.

Results: Age-related declines in CRF were observed in men with and without T2DM. For men younger than 60 years, at low-mid percentiles of the CRF distribution the magnitude of the age-related decline in CRF was significantly higher (*P*-values=.00, .02) in men with T2DM than in those without T2DM. At upper percentiles, the decline with age between the 2 groups was virtually identical. Significant declines in CRF in men 45 years or younger were observed only at high levels of CRF for those without T2DM and at low levels of CRF for those with T2DM (*P*-values .00, .04).

Conclusion: This study reported that men younger than 60 years with T2DM at the low-mid CRF percentiles experience an accelerated age-related decline in CRF. Men younger than 60 years with T2DM exhibiting high levels of CRF experienced a decline in CRF comparable to men without T2DM. This study highlights the importance of incorporating sufficient levels of exercise or activity to maintain high CRF in men with T2DM.

Unequivocal evidence indicates that higher cardiorespiratory fitness (CRF) reduces the risk of several non-communicable diseases (NCDs) and mortality in US adults.[1-3] Importantly, previous studies observed similar associations in individuals with type 2 diabetes mellitus (T2DM), a clinical subgroup representing nearly 10% of US adults.[4,5] Thus, as recommended by the American Heart Association, attaining a higher CRF level via regular moderate-to-vigorous exercise training is critical to the health and quality of life of individuals with T2DM.[6,7]

However, of concern, studies report that CRF declines with age.[8,9] The onset of this age-related decline occurs near 40 years and persists between 6% and 10% per decade of life.[10] Consequently, these reductions in CRF may be partially explained by the significant age-related reductions in cardiovascular function, subsequently increasing prevalence of NCDs found in middle-aged and older adults. Fortunately, consistent evidence indicates that attaining higher CRF, ideally earlier in life,[11] may attenuate this age-related decline potentially preventing or delaying the onset of NCDs.[12,13] Although this evidence provides a template for improving the health of US adults across the life span, it is based on studies conducted in "apparently healthy" US adults. Thus, whether this age-related decline in CRF is present or possibly exacerbated in individuals with

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an NCD such as T2DM remains unclear. Furthermore, less is known about whether higher CRF is associated with a slower age-related decline in this clinical population.

Assessing the extent to which these well-documented associations exist in adults with and without T2DM may provide further insight on the clinical significance of CRF. Thus, the purpose of this study was to evaluate the association between age and CRF, estimated using a maximal treadmill test, in adults with and without T2DM. This study used quantile regression, a comprehensive statistical method, which allowed for a thorough analysis of the association between age and CRF in individuals with and without T2DM across many adjusted CRF percentiles. This study focuses only on adult men as the sample size for women in the Aerobics Center Longitudinal Study (ACLS) data set (particularly for women with diabetes) was not sufficient for such a detailed analysis.

PATIENTS AND METHODS

The ACLS is a prospective observational study of individuals who completed comprehensive medical examinations at the Cooper Clinic in Dallas, Texas.[14] Study participants came to the clinic for periodic preventive health examinations and for counseling regarding diet, exercise, and other lifestyle factors associated with an increased risk of chronic disease. Between 1974 and 2006, participants received at least 1 comprehensive medical examination and maximal graded treadmill exercise test at the clinic. Most study participants were non-Hispanic white from middle to upper socioeconomic strata and were referred by either their employers or physicians, or by themselves. The study was reviewed and approved annually by the Cooper Institute's Review Board, and all participants provided written informed consent. The data set used for the present study included 35,307 men (total observations, 74,144; average number of visits, 2.10). Among these, 12,951 (37%) participants had more than 1 visit.

Measures

The comprehensive health evaluation is described in detail elsewhere.[15,16] The outcome of interest in this study was CRF, which was estimated with a maximal treadmill exercise test using a modified Balke protocol.[17] The treadmill speed was 88 m/min initially, and participants began the test at 0% grade. The grade was increased to 2% for the second minute and was thereafter increased 1% per minute until the 25th minute. After 25 minutes, the speed was increased to 5.4 m/min without a grade change until test termination. All participants were encouraged to put maximal effort during the test. Participants who had the test ceased by a physician for problematic signs and symptoms or failed to reach 85% of age-predicted maximal heart rate were excluded from the analyses to ensure that near maximal effort was obtained. Maximum oxygen consumption (VO_2max) scaled to lean body mass was estimated from the final treadmill grade and speed by using the Fitness Registry and the Importance of Exercise National Database equation: $(speed \times 0.17) + (speed \times grade \times 0.79) + 3.5$.[18] Diabetes status was determined in accordance with the American Diabetes Association guidelines by using either of the following 2 criteria[19]: (1) a fasting-plasma glucose level of 7 mmol/L or higher (126 mg/dL or higher) reported at a clinical follow-up evaluation or (2) a response to a health survey indicating that the participant either was currently taking hypoglycemic medication or was diagnosed with T2DM by their physician.

Statistical Analyses

Stata version 12 (StataCorp LLC) was used for all statistical analyses. Cardiorespiratory fitness (ie, VO_2max scaled to lean body mass) was treated as the dependent variable for all regression analyses. Quantile regression[20] was used to assess the associations between CRF and age at the 10th, 25th, 50th, 75th, and 90th CRF percentiles. Regression models with age treated continuously were used to assess differences in the association between age and CRF between persons with and without diabetes via 2-way interaction terms between age and diabetes status. Previous studies[8,9] using mean regression suggest that the decline in fitness with age indicates a substantial departure from linearity. To account for this, a linear spline model with knots at 45 and 60 years of age were used in the quantile regression analyses to allow the slope of the relationship between CRF and age to change at these points. The model with knots at 45 and 60

years exhibited slightly better overall fit across CRF percentiles than did a corresponding quadratic model and other 2- and 3-knot spline models with knots placed at 5-year increments from 40 to 70 years. To provide additional easily interpretable and intuitively meaningful estimates of the magnitude of associations between age and CRF for adults both with and without diabetes, regression models for the 10th, 50th, and 90th percentiles of CRF, treating age as a categorical predictor stratified by diabetes status, were also used. For analyses in which age was categorized, age was divided into 7 levels, less than 40 years (referent level), 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, and 70 years and older. Smoking status and birth cohort were adjusted for in all regression models because of an established relationship with age and/or CRF. Smoking status (current smoker or not) was obtained from a standardized questionnaire. Birth cohort was based on each participant's year of birth categorized into 4 groups: 1930 or earlier, 1931 to 1940, 1941 to 1950, and after 1950. The primary modifiable factor determining an individual's CRF level is regular moderate-to-vigorous physical activity. Results from an additional analysis stratified by self-reported physical activity levels (sedentary, moderate, and high) are provided in the Supplemental Appendix (available online at http://www.mcpiqojournal.org).

Multiple observations for the same subject are unlikely to be independent. The quantile regression estimator is consistent when the data are not independent,[21] and the method of Parente and Santos Silva[22] (implemented via the qreg2 command in Stata) was used to account for this potential nonindependence for SE and CI estimation. Quantile regression coefficients are interpreted similarly to those of ordinary linear regression coefficients except that a quantile regression coefficient indicates the change in the value at the modeled percentile, not the mean, of the dependent variable. For example, consider the categorical predictor for age with 7 categories and a referent level of less than 40 years. A coefficient estimate of −4 for people aged 60 to 64 years in the quantile regression model for the 90th percentile would indicate that the 90th percentile of CRF (the outcome variable) is estimated to be 4 mL of O_2 per kilogram per minute less for people

aged 60 to 64 years as compared with those younger than 40 years after controlling for other covariates in the model.

RESULTS

The sample characteristics for adult men at the first health examination with and without T2DM are presented in Table 1. Across percentiles, unadjusted point estimates of CRF percentiles for those without T2DM were higher than the corresponding point estimates for those with T2DM.

The adjusted regression coefficients evaluating differences in age-related decline in CRF between individuals with and without T2DM are presented in Table 2. In general, estimated SEs for point estimates were smaller for middle percentiles. For adult men without T2DM, the estimated slope relating CRF and age, up to an age of 45 years, was significant and positive at the 10th, 25th, and 50th CRF percentiles (P-values=.00, .00, .00), with the magnitude of the estimates decreasing as CRF percentiles increased. In contrast, a significant negative slope was observed at the 90th percentile (P-value=.00). For men between 45 and 60 years of age as well as those older than 60 years, the slope estimates were significant and negative for all CRF percentiles (P-values all=.00), with the magnitude of the estimates increasing with increasing percentiles. Estimates for the decline in CRF per year of age ranged from 0.07 to 0.26 mL of O_2 per kilogram per minute.

For adult men with T2DM, the estimated slopes relating CRF and age, up to an age of 45 years, were all negative, although only the slope at the 10th CRF percentile was significant (P-value=.04). For men between 45 and 60 years of age, the slope estimates were significant (P-values=.01, .00, .00, .00, .00) and negative for all CRF percentiles, with the magnitude of the estimates increasing with increasing percentiles. The estimated decline in CRF per year of age ranged from 0.06 to 0.18 mL of O_2 per kilogram per minute. For men older than 60 years, the slope estimates were significant (all P-values=.00) and negative for all CRF percentiles, with the magnitude of the estimates decreasing with increasing percentiles for percentiles higher than 25th. The estimated decline in CRF per

	No diabetes	Diabetes
TABLE 1. Sample Characteristics for Participants at Their First Medical Examination Comparing Adult Men With and Without Diabetes (N=35,307)[a,b,c]		
Characteristic	(n=33,742)	(n=1565)
Vo$_2$max (mL/min per kilogram)		
25th percentile	37.8	36.0
50th percentile	40.1	38.5
75th percentile	42.5	40.8
Age (y)		
25th percentile	38.0	43.0
50th percentile	44.0	50.0
75th percentile	51.0	56.0
Birth cohort		
<1931 (referent)	3770 (11)	279 (18)
1931-1940	7068 (21)	332 (21)
1941-1950	11,434 (34)	456 (29)
>1950	11,470 (34)	498 (32)
Smoke		
No (referent)	28,158 (83)	1312 (84)
Yes	5584 (17)	253 (16)
Age categories		
<40 y	10,976 (32)	221 (14)
40-44 y	7071 (21)	251 (16)
45-49 y	6077 (18)	306 (20)
50-54 y	4564 (14)	311 (20)
55-59 y	2839 (8)	226 (14)
60-64 y	1392 (4)	150 (10)
65-69 y	558 (2)	62 (4)
≥70 y	265 (1)	38 (2)

[a]Vo$_2$max, maximum oxygen consumption.
[b]Data are presented as mean, percentile, or No. (percentage).
[c]Aerobics Center Longitudinal Study data collected in the United States from 1974 to 2006.

year of age ranged from 0.17 to 0.23 mL of O$_2$ per kilogram per minute.

Significant differences in the slopes relating age and CRF between those with and without T2DM were observed for several adjusted percentiles (P-values=.00, .02, .01) of CRF (ie, at percentiles of 10th, 50th, and 90th); however, a difference in the trend of these differences was observed across percentiles. At the 10th percentile of CRF, the estimated age-related decline in fitness for men 45 years or younger with diabetes was significantly greater (P-value=.00) than for men without diabetes. Similarly, at the 50th percentile of CRF, the estimated age-related decline in fitness for men aged 45 to 60 years with diabetes was significantly greater (P-value=.02) than for men without diabetes. However, at the 90th percentile of CRF, the

estimated age-related decline in fitness for men older than 60 years of age with diabetes was significantly less (P-value=.01) than for men without diabetes. The estimated slope coefficients for age ranges up to 45 years and for 45 to 60 years for both persons with and without T2DM from this analysis are plotted in Figure 1, and the slope estimates for the age 60 years and older are plotted in Figure 2.

Age and CRF: Stratified Analyses by T2DM Status

Adult Men Without T2DM. Adjusted estimated differences in CRF by 5-year age groups for adult men without T2DM are presented in Table 3. Adult men without T2DM younger than 40 years served as the referent group for all comparisons. For 40- to 44-year-old adult men without T2DM, a significant increase in CRF (P-values=.00, .00) was observed for 10th and 50th percentiles with the magnitude of estimated differences decreasing with increasing percentiles. In contrast, a significant decrease in CRF was observed for the 90th percentile (P-value=.00). For 45- to 49-year-olds, a significant decrease in CRF was observed only at the 90th percentile (P-value=.00). For 50- to 54-year-olds, significant decreases in CRF were observed at the 50th and 90th percentiles (P-values=.00, .00). For all remaining age groups, significant decreases in CRF were observed across all percentiles (all P-values=.00). For all these remaining age groups, the magnitude of the estimated decrease in CRF increased uniformly with increasing CRF percentiles from a minimum of 0.48 to a maximum of 7.06 mL of O$_2$ per kilogram per minute.
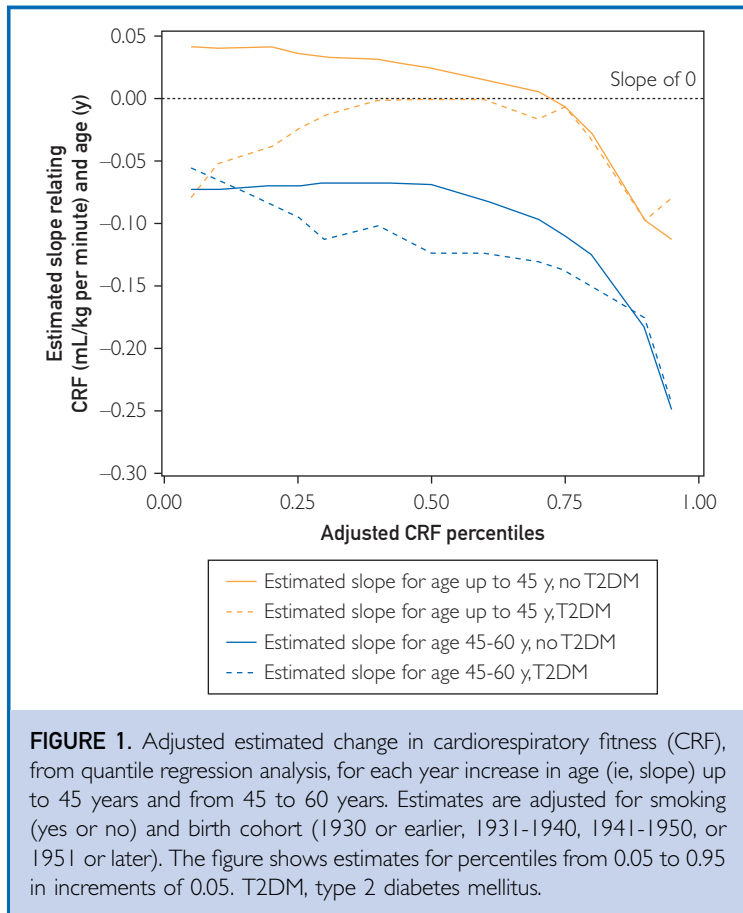
Adult Men With T2DM. Adjusted estimated differences in CRF by 5-year age groups for adult men with T2DM are presented in Table 3. Adult men younger than 40 years with T2DM served as the referent group for all comparisons. For 55- to 59-year-old adult men with T2DM, significant decreases in CRF were observed for the 50th and 90th percentiles (P-values=.02, .04) of CRF with point estimates of 1.06 and 1.43 mL of O$_2$ per kilogram per minute, respectively. For 60- to 64- and 65- to 69-year-old adult men with T2DM, significant decreases in CRF were observed for all CRF percentiles (P-values=.04, .00, .01, .00, .00, .00, .00), with the magnitude

TABLE 2. Quantile Regression Estimates (Est.) for Age Along With a 2-Way Interaction Between Age and Diabetes Along With 95% CIs for Select Cardiorespiratory Fitness Percentiles[a,b]

	Percentile									
	10th		25th		50th		75th		90th	
Variable	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI	Est.	95% CI
No diabetes										
Age, ≤45 y	**0.04**	**0.03 to 0.05**	**0.04**	**0.03 to 0.05**	**0.02**	**0.01 to 0.03**	−0.01	−0.02 to 0.01	**−0.10**	**−0.12 to −0.07**
Age, 45-60 y	**−0.07**	**−0.09 to −0.06**	**−0.07**	**−0.08 to −0.06**	**−0.07**	**−0.08 to −0.06**	**−0.11**	**−0.12 to −0.10**	**−0.18**	**−0.21 to −0.16**
Age, >60 y	**−0.20**	**−0.24 to −0.17**	**−0.21**	**−0.23 to −0.19**	**−0.24**	**−0.27 to −0.22**	**−0.24**	**−0.27 to −0.22**	**−0.26**	**−0.30 to −0.22**
Diabetes										
Age, ≤45 y	**−0.05**	**−0.10 to −0.00**	−0.03	−0.09 to 0.04	0.00	−0.05 to 0.05	−0.01	−0.10 to 0.09	−0.10	−0.24 to 0.05
Age, 45-60 y	**−0.06**	**−0.12 to −0.01**	**−0.10**	**−0.14 to −0.06**	**−0.12**	**−0.17 to −0.08**	**−0.14**	**−019 to −0.09**	**−0.18**	**−0.28 to −0.08**
Age, >60 y	**−0.21**	**−0.29 to −0.12**	**−0.23**	**−0.29 to −0.17**	**−0.20**	**−0.28 to −0.11**	**−0.18**	**−0.25 to −0.10**	**−0.17**	**−0.23 to −0.10**
Difference in slopes										
Age, ≤45 y	**−0.09**	**−0.15 to −0.04**	−0.06	−0.13 to 0.01	−0.02	−0.08 to 0.03	0.00	−0.10 to 0.10	0.00	−0.14 to 0.14
Age, 45-60 y	0.01	−0.04 to 0.06	−0.03	−0.07 to 0.02	**−0.05**	**−0.10 to −0.01**	−0.03	−0.08 to 0.02	0.01	−0.09 to 0.11
Age, >60 y	0.00	−0.09 to 0.08	−0.02	−0.08 to 0.04	0.05	−0.04 to 0.14	0.07	−0.01 to 0.15	**0.09**	**0.02 to 0.17**

[a]Differences in slopes calculated as slope for persons with diabetes minus slope for persons without diabetes. Estimates are in milliliters per minute per kilogram per year.

[b]Coefficients in boldface indicate significant findings at $P<.05$. Estimates are adjusted for smoking (yes or no) and birth cohort (1930 or earlier, 1931-1940, 1941-1950, or 1951 or later). The referent level for birth cohort is the group born 1930 or earlier. The cardiorespiratory fitness variable was scaled to lean body mass.

FIGURE 1. Adjusted estimated change in cardiorespiratory fitness (CRF), from quantile regression analysis, for each year increase in age (ie, slope) up to 45 years and from 45 to 60 years. Estimates are adjusted for smoking (yes or no) and birth cohort (1930 or earlier, 1931-1940, 1941-1950, or 1951 or later). The figure shows estimates for percentiles from 0.05 to 0.95 in increments of 0.05. T2DM, type 2 diabetes mellitus.

of the point estimates increasing with increasing CRF percentiles and ranging from 1.34 to 3.51 mL of O_2 per kilogram per minute. For adult men 70 years or older with T2DM, significant decreases in CRF were observed for all CRF percentiles (all P-values=.00), with point estimates remaining approximately constant, ranging from 3.33 to 3.36 mL of O_2 per kilogram per minute.

DISCUSSION

The purpose of this study was to comprehensively evaluate the association between age and CRF (ie, Vo_2max scaled to lean body mass), estimated using a maximal treadmill test, in adult men with and without T2DM. The first major finding of this study was that the magnitude of the decline in fitness associated with aging was significantly greater (P-values=.00, .02) for adult men with T2DM than for men without T2DM at the lower tail and center of the adjusted CRF distribution (ie,

10th and 50th CRF percentiles) for the age range up to 45 and 45 to 60 years, respectively. Although at the upper CRF percentiles (ie, 90th percentile), the decline in fitness associated with age between the 2 groups were virtually identical until about 60 years, where the age related decline for those with T2DM was significantly less than for those without T2DM (P-value=.01). This suggests that maintaining at least a moderate CRF level may be particularly important in diminishing the accelerated age-related decline in this subpopulation. Second, the expected significant age-related decline in CRF in men in age groups 40 to 44 and 45 to 49 years was observed only at high levels of CRF (ie, 90th percentile) for adult men without T2DM (P-values=.00, .00).

To our knowledge, this is the first study to document a differential age-related decline in CRF between men with and without T2DM. Although novel, this accelerated age-related decline in CRF in adult men with T2DM at low-to-mid levels of CRF was not unexpected. Several studies have previously documented that T2DM negatively affects the normal aging process with exaggerated decreases in mitochondrial,[23] respiratory,[24] and cardiovascular[25,26] function. Regarding the last, several studies observed greater declines in vascular compliance, endothelial function, arterial blood flow, diastolic function, myocardial fibrosis, impaired coronary artery blood flow, and others. Research suggests that the accelerated aging of the cardiovascular system may be consequent to the higher levels of oxidative stress,[27] glycated hemoglobin,[28] and insulin resistance observed in individuals with T2DM. Optimal function of the cardiovascular system is paramount to maintaining higher levels of maximal aerobic capacity (ie, CRF) across the life span. As such, the augmented aging of the cardiovascular system in individuals with T2DM potentially facilitates and explains their accelerated age-related decline in CRF observed in this study. This enhanced age-related decline suggests that lower-fit individuals may be predisposed to an increased risk of NCDs and premature mortality.

Interestingly, this study also reported that adult men 60 years and younger with T2DM at high levels of fitness (ie, 90th percentile) exhibit a similar age-related decline in CRF as their high-

fit counterparts without T2DM. As shown in Figure 1, by the 90th percentile the difference in slope coefficients estimating the yearly change in CRF between adult men with and without T2DM was near zero. As shown in Figure 2, for men 60 years and older, by the middle CRF percentiles the trend was reversed with the estimated yearly reduction in CRF for adult men with T2DM less (although not significantly less) than the corresponding estimate for men without T2DM with the estimated differences increasing and becoming significant by the 90th percentile (*P*-value=.01). Clinically, this observation indicates the importance of adult men with T2DM achieving a high level of CRF. Previous studies reported that short-term aerobic exercise training (eg, 3-8 months), the only modifiable behavior consistently found to increase CRF, significantly enhanced cardiovascular function in individuals with T2DM with specific improvements in coronary and systemic endothelial function and reduced diastolic dysfunction and arterial stiffness.[29] Given this, participating in aerobic or aerobic+resistance exercise training, likely leading to increased levels of CRF, may attenuate the age-related decline in CRF[30] such that it becomes essentially indistinguishable from the age-related decline observed in adult men without T2DM. Consequently, individuals with T2DM may have a risk of premature cardiovascular disease mortality no higher than their counterparts without T2DM.

Unexpectedly, our study also reported that the onset of the decline in CRF expected at the fourth decade of life was observed only in the highest-fit adult men without T2DM (ie, 90th percentile) and in the lowest-fit men with T2DM (ie, 10th percentile). In this large sample (>70,000 observations for persons without T2DM), we expected to observe a significant decrease in CRF across most, if not all, of the CRF distribution, as previous studies reported the average age of the decline in CRF occurs between the ages of 40 and 45 years.[10] Two concepts may explain this observation. First, previous studies evaluating the age-related decline in CRF restricted their analyses to assessing the *average* decline in CRF associated with age. However, a mean regression analysis averages across all percentiles and so may suffer from a substantial loss of information if there are substantial differences in the nature of the
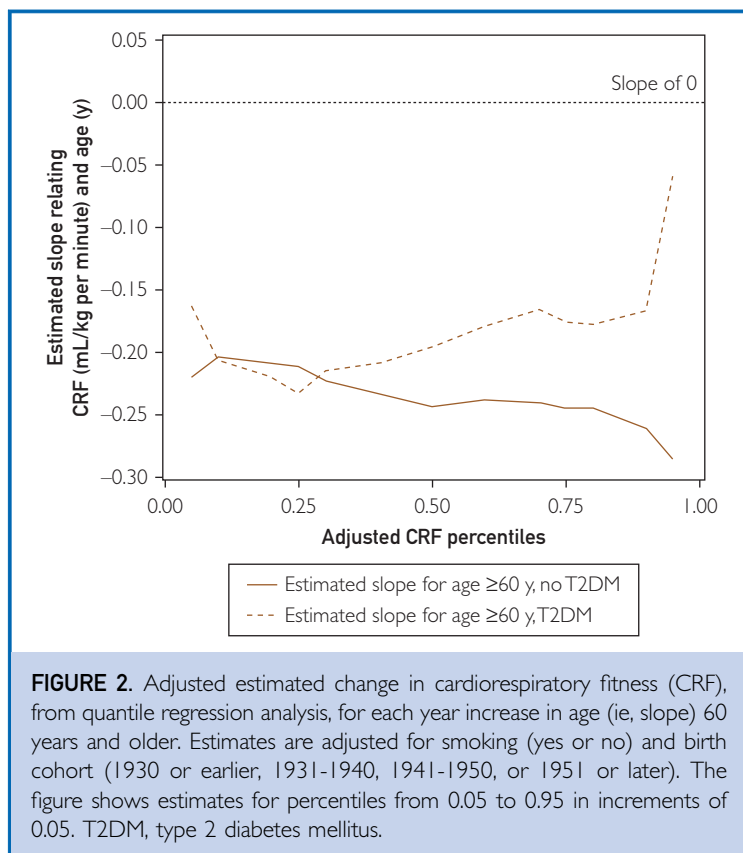

FIGURE 2. Adjusted estimated change in cardiorespiratory fitness (CRF), from quantile regression analysis, for each year increase in age (ie, slope) 60 years and older. Estimates are adjusted for smoking (yes or no) and birth cohort (1930 or earlier, 1931-1940, 1941-1950, or 1951 or later). The figure shows estimates for percentiles from 0.05 to 0.95 in increments of 0.05. T2DM, type 2 diabetes mellitus.

association of interest across percentiles. Uniquely, the use of quantile regression[31-33] in this study permitted a more comprehensive examination of the influence of age on CRF, allowing an assessment across multiple percentiles of the CRF distribution. For adult men both with and without T2DM in the combined analysis, a significant decrease in CRF per year was observed for those older than 45 years across all CRF percentiles (all *P*-values .01 or less), whereas for those 45 years and younger, significant reductions in CRF per year were observed only at the 10th and 90th percentiles (*P*-values=.04, .00) of CRF for those without and with T2DM, respectively. These findings expand the existing scientific literature, suggesting that for adult men without T2DM perhaps the onset of a significant age-related decline in CRF may occur primarily in the 5th as opposed to the 4th decade of life for all but those at the highest fitness levels (less than or equal to adjusted 90th CRF percentiles). Although for adult men with T2DM, a significant age-related decline in CRF may occur in the 4th decade but be primarily limited to those

TABLE 3. Estimated Differences in Cardiorespiratory Fitness (Est.) for Each 5-Y Age Group, as Compared With Persons Younger Than 40 Y, Along With 95% CIs for Select Cardiorespiratory Fitness Percentiles[a,b]

| | Percentile | | | | | |
| | 10th | | 50th | | 90th | |
Variable	Est.	95% CI	Est.	95% CI	Est.	95% CI
No diabetes						
Age, 40-44 y	**0.34**	**0.20 to 0.48**	**0.19**	**0.08 to 0.31**	**−0.54**	**−0.80 to −0.28**
Age, 45-49 y	0.09	−0.06 to 0.24	−0.01	−0.14 to 0.11	**−1.47**	**−1.76 to −1.18**
Age, 50-54 y	0.06	−0.11 to 0.22	**−0.29**	**−0.42 to −0.15**	**−2.31**	**−2.62 to −2.01**
Age, 55-59 y	**−0.48**	**−0.69 to −0.26**	**−0.59**	**−0.75 to −0.42**	**−3.06**	**−3.39 to −2.73**
Age, 60-64 y	**−1.18**	**−1.45 to −0.91**	**−1.29**	**−1.50 to −1.09**	**−4.05**	**−4.45 to −3.66**
Age, 65-69 y	**−1.94**	**−2.26 to −1.62**	**−2.37**	**−2.62 to −2.12**	**−5.50**	**−5.98 to −5.02**
Age, ≥70 y	**−3.62**	**−4.04 to −3.22**	**−4.08**	**−4.42 to −3.75**	**−7.06**	**−7.71 to −6.41**
Diabetes						
Age, 40-44 y	0.17	−0.74 to 1.09	0.32	−0.31 to 0.95	0.07	−1.26 to 1.41
Age, 45-49 y	−0.52	−1.58 to 0.54	−0.46	−1.15 to 0.24	−0.64	−1.96 to 0.68
Age, 50-54 y	−0.87	−1.94 to 0.20	−0.47	−1.26 to 0.33	−0.86	−2.18 to 0.45
Age, 55-59 y	−0.46	−1.66 to 0.74	**−1.06**	**−1.92 to −0.21**	**−1.43**	**−2.83 to −0.03**
Age, 60-64 y	**−1.34**	**−2.61 to −0.06**	**−1.64**	**−2.57 to −0.70**	**−2.02**	**−3.45 to −0.59**
Age, 65-69 y	**−2.32**	**−3.61 to −1.03**	**−2.73**	**−3.97 to −1.49**	**−3.51**	**−5.18 to −1.85**
Age, ≥70 y	**−3.36**	**−5.14 to −1.57**	**−3.33**	**−4.65 to −2.01**	**−3.35**	**−5.47 to −1.22**

[a]Estimates are in milliliters per minute per kilogram per year.

[b]Coefficients in boldface indicate significant findings at $P<.05$. Estimates are from regression models stratified by diabetes status and adjusted for smoking (yes or no) and birth cohort (1930 or earlier, 1931-1940, 1941-1950, or 1951 or later). The referent level for birth cohort is the group born 1930 or earlier. The sample sizes were 71,371 and 2773 (number of observations) for those without and with diabetes, respectively. The cardiorespiratory fitness variable was scaled to lean body mass.

with the lowest levels of CRF. Second, it is possible that a significant decrease in CRF in persons in their early forties was observed in men only at the adjusted upper CRF percentiles because these adults are at an optimal level of CRF.[34] Correspondingly, their cardiopulmonary systems may be more sensitive to the initial subtle changes in the aging process, such as decreases in the number of cardiac myocytes, cardiac output, lean muscle mass, and pulmonary diffusion capacity,[35] resulting in a significant and larger reduction in CRF compared with their lower-fit counterparts. Despite having a larger loss in CRF, due to their higher level of CRF at the onset of this decline, high-fit individuals have lower risks of several NCDs and mortality as they age than do their low-fit counterparts.[14,15]

This study has several strengths. Uniquely, to our knowledge, this is the first study to evaluate and document that adult men with T2DM have an accelerated age-related decline in CRF and that achieving a high level of CRF may diminish this accelerated age-related decline. These observations are clinically relevant, providing evidence for the need to incorporate

physical activity at levels sufficient to maintain a high CRF level in the male population with diabetes. Moreover, this study used data from the ACLS prospective cohort, providing a large sample size and used the Fitness Registry and the Importance of Exercise National Database equation to estimate CRF, an equation found to predict CRF with greater precision as compared with the traditional American College of Sports Medicine equations.[18] Lastly, the employment of quantile regression analyses allowed for a comprehensive analysis of the association between age and CRF in adult men with or without T2DM. Consequently, this technique led to unprecedented findings regarding the age-related decline in CRF in adult men with T2DM and expanded the existing literature regarding the onset of the age-related decline in CRF in adult men without T2DM. In addition to these strengths, this study has some limitations. First, ideally a direct measurement of CRF would have been available for the analysis; however, because this was not available for this large sample, CRF was estimated using a maximal treadmill test. Second, despite the large sample, the ACLS cohort includes mostly non-Hispanic white

men from the upper socioeconomic strata, with a comparatively small percentage of observations for persons with T2DM, reducing the generalizability of our findings. Third, the study design does not allow any causative inferences to be made from our findings. Lastly, our analyses did not account for the use of medications that potentially influence CRF.

CONCLUSION

This study reports 2 clinically relevant observations with regard to age and CRF in adult men with T2DM. First, our findings suggest that adult men, up to 45 years of age and from 45 to 60 years of age, with T2DM at the adjusted lower to middle CRF percentiles experience an accelerated age-related decline in CRF as compared with adult men (of the same age) without T2DM, likely predisposing these individuals to an augmented risk of NCDs and premature cardiovascular disease mortality. Second, adult men with T2DM, up to 45 years of age and from 45 to 60 years of age, exhibiting the highest levels of CRF (ie, 75th and 90th percentiles) appeared to reduce this accelerated age-related decline in CRF relative to their counterparts of the same age without T2DM. The findings of this study reinforce the requisite incorporation of sufficient levels of exercise training necessary to improve CRF, especially in this clinical subpopulation and ideally before the onset of the decline in CRF and subclinical cardiovascular abnormalities associated with T2DM. In addition, given the lack of diversity of the ACLS data, it is of particular importance for future research to explore this research question in other subpopulations including women, those of lower socioeconomic status, and more diverse racial/ethnic groups.

ACKNOWLEDGMENTS

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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Potential Competing Interests: The authors report no competing interests.

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