Summer 2019

The Association of Cardiorespiratory Fitness with Advancing Age Among Those With and Without Type II Diabetes

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THE ASSOCIATION OF CARDIORESPIRATORY FITNESS WITH ADVANCING AGE AMONG THOSE WITH AND WITHOUT TYPE II DIABETES

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Bachelor of Science
University of North Florida, 2014

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in Public Health in

Epidemiology

The Norman J. Arnold School of Public Health

University of South Carolina

2019

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ACKNOWLEDGEMENTS

I would like to acknowledge the patience and understanding bestowed to me by my thesis committee, the encouragement provided by my coworkers and colleagues, especially Dr. Jennifer Duffy, the cheering and rallying from my peers from the Department of Epidemiology and Biostatistics at the University of South Carolina, and all the love and support provided to me by my family and friends. I am truly surrounded by the best support system I could have ever hoped for.

ABSTRACT

OBJECTIVE: This study examined the relationship between cardiorespiratory fitness (CRF) and age to determine if the decrease in CRF associated with advancing age is greater among those with type 2 diabetes mellitus (T2DM) as compared to those without T2DM. This study also assessed if differences in CRF between persons with T2DM and those without are consistent across CRF percentiles.

METHODS: Data from the Aerobics Center Longitudinal Study (ACLS, Dallas, Texas, 1970-2006) were utilized in the current study. CRF was measured by maximal treadmill exercise testing using the Balke protocol and T2DM status was determined by self-report of previous diagnosis by a physician, a fasting glucose of >126 mg/dL, or insulin use. Multivariable linear regression was performed to assess the association between CRF and age taking into account the interaction between T2DM status and age and adjusting for potential confounding variables. Additionally, quantile regression was performed to estimate the association between the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of CRF and T2DM status.

RESULTS: The 12,648 predominantly non-Hispanic white, well-educated, and middle-to-upper socio-economic status men included in the sample with an average of 3.63 visits resulted in 49,704 complete observations (568 from those with T2DM). In the linear regression analyses, the interaction between T2DM status and age was statistically significant. For those with T2DM, the decrease in CRF is an additional 0.020 METs per one-year increment of age as compared to those without T2DM. Across the 5^{th}, 10^{th}, 25^{th}, 50th, and 75th percentiles of CRF, diabetics had significantly lower CRF (-0.594, -0.456, -0.464, -0.333, -0.207 respectively) compared to non-diabetics.

CONCLUSIONS: This study show that the decrease in CRF associated with age was greater those with T2DM compared to those without T2DM. Through understanding the relationship between CRF and advancing age for those with and without T2DM, as well as understanding the differences between T2DM and CRF across the entire distribution of CRF, we can better tailor physical fitness interventions for populations looking to reduce the occurrence of diseases known to be associated with CRF.

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LIST OF ABBREVIATIONS

ACLS .... Aerobics Center Longitudinal Study

ADA .... American Diabetes Association

BMI .... Body Mass Index

CI.. Confidence Interval

CRF .... Cardiorespiratory Fitness

PA .... Physical Activity

MET .... Metabolic Equivalent

MetSyn .... Metabolic Syndrome

NIDDM .... Non-Insulin Dependent Diabetes Mellitus

T2DM .... Type 2 Diabetes Mellitus

CHAPTER 1

INTRODUCTION

1.1 Statement of Problem

The International Diabetes Federation identified in 2015 that 1 in 11 adults are living with diabetes, and that by the year 2040, they expect this statistic to rise to 1 in 10 adults (Ogurtsova et al., 2017). This dramatic increase is often believed to be due to aging populations with sedentary lifestyles and continued urbanization worldwide (Wild, Roglic, Green, Sicree, & King, 2004). Increased prevalence of diabetes in a population has many implications such as an increased economic burden and a lower quality of life amongst afflicted individuals (American Diabetes Association, 2013).

It has been established in the literature that as individuals age, body mass index (BMI, kg/m^2), waist circumference, and other measures of adiposity increase. This has been shown to be exacerbated by age-related decreases in physical activity and muscle mass (Rosen, Sorkin, Goldberg, Hagberg, & Katzel, 1998; Toth, Gardner, Ades, & Poehlman, 1994). An aging population with an increased BMI is most at risk for obesity and developing metabolic syndrome (MetSyn), type 2 diabetes mellitus (T2DM), and other morbidities. T2DM is associated with an increased risk of mortality along with coronary heart disease, stroke, renal disease, hypertension, and other chronic diseases (Eyre et al., 2004). However, T2DM is a disease whose burden can be decreased by early detection and the implementation of preventative measures (Katzmarzyk, Craig, & Gauvin, 2007).

Physical inactivity, obesity, and diet are considered the biggest modifiable risk factors for the development of T2DM (Eyre et al., 2004). In a study conducted by Borodulin et. al., it was found that including birth cohort in the predictive model showed differences between physical activity and age between birth cohorts (Borodulin, Laatikainen, Juolevi, & Jousilahti, 2007). Olsen et al. posited that controlling for birth cohort highlighted circumstances experienced by these cohorts and not experienced by others (Olsen, Baker, Holst, & Sørensen, 2006).

Cardiorespiratory fitness (CRF) is defined as the maximum uptake of oxygen consumption (VO_2 max) measured as mL/kg per minute (Blair et al., 1989). This is widely considered to be an accurate determination of aerobic capacity (Aadahl, Kjær, Kristensen, Mollerup, & Jørgensen, 2007). Because of its ability to function as an objective measure of habitual physical activity, CRF has been used as a predictor of potential adverse health outcomes in many epidemiological studies (Barlow et al., 2005; Carnethon et al., 2009; Després, 2016). High levels of CRF has been found to be a protective factor against the development of MetSyn (Laaksonen et al., 2002), hypertension in women (Barlow et al., 2005), and chronic kidney disease (Defina et al., 2013). Looking at a longitudinal analysis of repeated measures of CRF, Blair et al. found that men who were unfit at an initial measurement visit and then became fit, had a reduction in age-adjusted risk of all-cause mortality equal to roughly 44% when compared to men who were unfit at both visits. Those men who were fit at both visits saw a reduction in age-adjusted risk of all-cause mortality by about 66% (Blair et al., 1995). These results were then corroborated by a different study that examined whether or not the reduction in risk was due to real change or measurement error. It was found that the reduction in risk of all-cause mortality was not due to measurement error, but rather the results were a function of CRF, BMI, and resting heart rate (Jackson et al., 2004).

CRF has been shown to decline as individuals age (Hakola et al., 2011). It has been cited in the literature that maintaining physical activity, having a low BMI, and not smoking are associated with having higher CRF across the lifespan (Jackson, Sui, Hébert, Church, & Blair, 2009). However, having low CRF is associated with increased measures of abdominal obesity, and an increased risk for metabolic syndrome (Wedell-Neergaard et al., 2018). In light of a recent statement published by the American Heart Association recommending physicians to include routine measurement of CRF in practice for all adults, and the 2017 report citing an aging population that is experiencing increases in the prevalence of T2DM (Centers for Disease Control and Prevention, 2017), it is becoming increasingly important to understand the relationship between CRF and T2DM as individuals age.

1.2 Purpose and Specific Aims

The purpose of this study was to examine the relationship between CRF and age, and to determine if this relationship is different by T2DM status. We hypothesized that as individuals with T2DM age, they will have significantly lower levels of CRF than those without. We also hypothesized that these differences will not be consistent across percentiles of CRF.

The main study aims and objectives were as follows:

1. Determine if the decrease in CRF associated with age is significantly greater for those with T2DM compared to those without.

A) We hypothesized that decrease in CRF associated with age will be greater for individuals with T2DM than non-diabetics.

2. Assess if differences in CRF between persons with T2DM and those without are consistent across adjusted CRF percentiles.

   A) We hypothesized that individuals with T2DM will have significantly lower levels of CRF and these differences will lesson as the levels of CRF increase.

1.3 Significance of Research

Understanding how T2DM status effects physical fitness, measured objectively, is an important public health goal. Further, knowing if advancing age effects individuals with and without T2DM differently would be an integral part of designing and implementing studies or interventions for those afflicted with the condition. In this study, we sought to determine if the relationship of CRF, as an indicator of habitual physical activity, differs between individuals with and without T2DM. A significant difference between individuals with and without T2DM existing across adjusted quantiles for the entire distribution of CRF, could lead to differing recommendations and prescriptions of exercise.

1.4 Organization of Thesis

Background information on the main exposure and outcome of interest has been sufficiently provided in Chapter 1. Chapter 2 discusses the published literature focusing on the relationship between T2DM and CRF as an outcome. It also mentions the gaps in the literature and motivations for future epidemiological studies. Chapter 3 provides information on the analytical methodology employed, as well as potential confounders that might affect the study. The analysis was completed and interpreted with the results presented in Chapter 4. Final remarks, conclusions, and potential recommendations for future research are found in Chapter 5.

CHAPTER 2

LITERATURE REVIEW

2.1 Public Health Significance

The American Diabetes Association (ADA) estimates that in 2012, the estimated cost of diagnosed T2DM was $245 billion. People with T2DM had medical costs that were roughly 2.3 times those without T2DM. Of the estimated economic burden, $69 billion is associated with indirect costs, including absenteeism, reduced productivity, and lost productive capacity due to early death. The estimate only includes those with diagnosed T2DM and does not represent the individuals who suffer from undiagnosed T2DM, an estimated 27.8% of individuals with T2DM. From 2007 to 2012, a 41% increase in costs associated with T2DM was observed (Wild et al., 2004). Since there is expected to be a considerably strong growth in the prevalence of T2DM over the next 25 years (Wild et al., 2004), with the overall aging population driving this increase (Centers for Disease Control and Prevention, 2017), the economic burden associated with T2DM also can be expected to continue to increase.

T2DM is defined by elevated glycemic measures and is considered a strong risk factor for cardiovascular disease, which is the number one cause of death for those with T2DM, as well as the leading cause of death in the United States (American Diabetes Association, 2013). In 2010, the American Diabetes Association amended the screening for T2DM to include an elevated measure of glycated hemoglobin (A_{1c}) of at least 6.5

percent (Fox et al., 2015). Fox et al. found that this change has increased screening capacity and has allowed for a more accurate depiction of individuals with the disease.

In a recent study conducted on a large United States insurance claims database by Weng et al., they found that the most frequent comorbidities associated with individuals diagnosed with T2DM and aged 18 years or older were hypertension, hyperlipidemia, cardiovascular diseases, neuropathy, nephropathy, and retinopathy (Weng et al., 2016). The ADA indicates that a critical component to the management and care of individuals with T2DM is to reduce those factors associated with cardiovascular disease, such as high blood pressure, high lipid levels, and tobacco use (Eyre et al., 2004). By limiting these factors and implementing healthy eating and physical activity habits, T2DM can be successfully treated.

2.2 Cardiorespiratory Fitness and Aging

The use of CRF has greatly impacted the field of exercise science (Ross et al., 2016). For example, this marker has proven to be a stronger predictor of mortality when compared to self-reported physical activity (D. C. Lee et al., 2011). CRF can be measured in maximal metabolic equivalents (METs) (Balke & Ware, 1959). Based on a recent meta-analysis, the reduction in mortality risk as associated with a 1-MET increase in exercise capacity ranges between 10% to 25% in both men and women and suggests that a higher level of fitness is associated with a lower risk of mortality (Kokkinos, 2012).

For the development of hypertension, MetSyn (which includes diagnostic criteria for T2DM), and hypercholesterolemia, CRF has shown to be strong predictor. In the study amongst healthy participants, Lee et al. found that those who maintained or improved fitness during a mean interval of 2.1 years, had a 26% lower risk of incident hypertension, a 42% lower risk of MetSyn, and a 26% lower risk of hypercholesterolemia when compared to participants who saw a decrease in CRF. Further, every MET increase from baseline to second examination was associated with a lower risk of 7%, 22%, and 12% in hypertension, MetSyn, and hypercholesterolemia, respectively (Duck Chul Lee et al., 2012).

Fleg et al. established that as age increases, there exists a substantial decline in peak VO_2 in healthy adults. The rate of decline in VO_2 was found to be not linear as individuals age. However, this decline was found to be stronger in men (Fleg et al., 2005). In a similar study, Jackson et al. utilized a cohort from the Aerobics Center Longitudinal Study (ACLS). It was found that longitudinal patterns of fitness were not linear across the lifespan. They observed a steep non-linear decline in CRF after age 45 for both men and women. This relationship remained significant after controlling for BMI, physical activity, and smoking behavior (Jackson et al., 2009). Unfortunately, the study was limited by a relatively short average follow-up of 7.9 years. Future studies should look at this longitudinal relationship with data that includes a much longer follow-up.

2.3 Association Between Cardiorespiratory Fitness and Type II Diabetes

The relationship between CRF and T2DM has been studied extensively in the past. In 1996, Lynch et al, examined the association between self-reported levels of the intensity and duration of physical activities (CRF) and incident cases of non-insulin dependent diabetes mellitus (NIDDM) in a Finnish population-based sample. After adjusting for the several known risk factors of NIDDM as confounders, they observed that an intensity of 5.5 metabolic units or greater and a duration of 40 minutes or greater per week reduced the risk of developing NIDDM by 56%. In a separate evaluation of just 'high risk' individuals, they found that these protective measures reduced their risk even further to 64% (Lynch et al., 1996).

With the understanding that physical inactivity and obesity are the two key players in the development of T2DM, Katzmarzyk sought to examine the relationship between several measures of adiposity and physical fitness, as measured in maximal METs, with incident T2DM in a Canadian cohort. They found that the measures of adiposity, as well as physical fitness, were significant predictors of T2DM after adjustment of several other well-known risk factors. Maximal METs were observed as being associated with a 70% lower odds of developing T2DM (OR = 0.30) after 15.5-years as determined by a follow-up survey (Katzmarzyk et al., 2007).

In 1999, Wei et al. published one of the first large prospective studies looking at the relationship between CRF and impaired fasting glucose (110-125 mg/dL) and incident T2DM. Wei et. al., found that after adjusting for age, parental T2DM, current smoking, alcohol use, and years of follow-up, men in the lowest 20% of CRF had 1.9 times the risk of developing impaired fasting glucose compared to men in the high-fitness group (top 20% of CRF) after a median 6.1-year follow-up. Results also showed that men in the low-fitness group had 3.7 times the risk of developing T2DM than men who were categorized in the high-fitness group (Wei et al., 1999).

Carnethon et al., studied the association of CRF with incident T2DM after a much longer 20-year follow-up from the Coronary Artery Risk Development in Young Adults (CARDIA) fitness study. They saw a higher rate of incident T2DM in black men and women as compared to white men and women over 20 years. However, after adjusting for BMI, baseline treadmill duration was found only to be significant with incident T2DM in white men. The participants who developed T2DM in the 20-year follow-up also were found to have experienced greater declines in fitness than those who did not acquire the disease (Carnethon et al., 2009).

In accordance with Wei's study, Sawada et al. used similar methods to determine the relationship between CRF and incident T2DM in a sample of Japanese men. After a much longer 14-year follow-up, and an adjustment for several well-known risk factors for T2DM, they observed that the high-fitness group had a 44% lower risk of developing T2DM when compared to the men in the lowest fit quartile (Sawada, Lee, Muto, Matuszaki, & Blair, 2003). This was the first study done on Japanese men to determine this strong inverse relationship between cardiorespiratory fitness and development of T2DM, independent of risk factors, including age, BMI, smoking status, and alcohol consumption.

In 2009, Lee et al. published a study examining the joint association between obesity and fitness with impaired fasting glucose and T2DM. It was observed that obese, as defined by having a BMI over 30 kg/m^2, and unfit men (least fit 20% of CRF) had 1.5 times the risk of developing impaired fasting glucose, and 5.7 times the risk of T2DM when compared to normal-weight and fit (the most fit 80%) men. A statistically significant difference was also observed between fit and unfit obese men. Obese and fit men had a significantly lower risk of developing T2DM compared to obese and unfit men (RR 0.47). This suggests that being fit might attenuate the risk of T2DM in obese men. In this study, fitness was categorized based on being unfit (lower 20% of fitness) or fit (upper 80% of fitness). Since the relationship between fitness and T2DM was assessed with fitness being dichotomized, future studies should look at how the entire distribution of fitness affects the risk of developing T2DM (Duck Chul Lee, Sui, Church, Lee, & Blair, 2009).

2.4 Summary

It has been largely established that in order to reduce T2DM and the negative implications it can have on an individuals' health, those diagnosed must maintain a healthy diet, reduce adiposity and high blood pressure, but also increase their habitual physical activity levels to therefore increase physical fitness (Ross et al., 2016). Previous studies have found that for each 1-MET increase in CRF, there was a 5% reduction in T2DM events (Zaccardi et al., 2015), and that the rate of decline in CRF is not linear, but instead accelerates with advancing age (Fleg et al., 2005). And although there is a well-documented association between physical activity and CRF and differences in physical activity and age amongst birth cohorts have been found in a previous study, current studies looking at the relationship between CRF and age have not taken birth cohort into account (Borodulin et al., 2007; Gossard et al., 1986; King, Haskell, Young, Oka, & Stefanick, 1995). In addition, it has not yet been determined whether T2DM status modifies the relationship between CRF and age.

Finally, most studies look at either T2DM or adverse cardiovascular events as the outcome with CRF as the predictor of interest (Carnethon et al., 2009; Katzmarzyk et al., 2007; Duck Chul Lee et al., 2009; Lynch et al., 1996; Sawada et al., 2003; Wei et al., 1999). Other studies examine the relationships holding CRF constant. In this study, we estimated the relationship between CRF and age among those with and without T2DM.

This estimates the relationship with CRF being dependent on age and T2DM status using linear regression. Through this, we are able to determine the effects of age and T2DM on changes in CRF. With this study, we also employed quantile regression, a non-parametric method to observe the entire distribution of CRF, to determine the differences in CRF for those with and without T2DM in a large homogeneous sample.

CHAPTER 3

RESEARCH METHODS

3.1 Study Population

The population utilized in this study was a subset of individuals who participated in a preventative medical examination and enrolled in the Aerobics Center Longitudinal Study (ACLS) at the Cooper Clinic in Dallas, Texas (Blair et al., 1989). ACLS is a prospective observational study of individuals who are predominantly non-Hispanic whites, well-educated, employed in or retired from professional positions, and of middle to upper socio-economic status. Men with medical examination visits from 1970 to 2006 were included in the current study in order to observe potential trends in CRF. Individuals with baseline T2DM (n=633), a history of heart attack (n=699), stroke (n=103), cancer (n=2438), or did not reach 85% of age-predicted maximal heart rate during treadmill test (n=1212) were excluded from the study. The final sample included 12,648 participants (ages 20 to 90) with 49,704 individual observations.

The Cooper Institute's institutional review board approved the study annually, with all participants providing a written informed consent for both the baseline examination and enrollment in the follow-up study.

3.2 Outcome of Interest

CRF was measured by a treadmill test during the medical examination of each visit for participants in the ACLS. This maximal exercise test was modified using the Balke protocol (Balke & Ware, 1959). Participants begin by walking at a speed of

88m/min without any elevation. After the first minute, elevation was increased by 2%. Elevation was increased another 1% per minute until the 25th minute. After 25 minutes, each minute, the speed increases by 5.4m/min until the end point of test. Maximal effort is encouraged to complete the test in order to receive an accurate measure of aerobic capacity (Blair et al., 1989).

3.3 Measures of Interest

The main exposure of this study was age (in years) to estimate the relationship between CRF and age. Additionally, comparisons were made between CRF and age among those with and without T2DM. In this sample, T2DM was defined per the American Diabetes Association criterion (fasting plasma glucose level of >126 mg/dL) (Fox et al., 2015). Patient's glucose levels were measured after an overnight fast at each medical examination. Individuals' observations with a fasting plasma glucose level of >126 mg/dL (n=349) or those who reported being previously diagnosed by a physician with T2DM (n=246) were classified as diabetic and included in the analysis (total n=568).

3.4 Covariates

Based off the literature review, several variables were identified as important to include in the analysis. These covariates are birth cohort (categorized based on participant's year of birth as before 1930, 1931-1940, 1941-1950, and after 1950), systolic blood pressure (mm Hg), fasting cholesterol (mg/dL), body fat percentage, physical activity (inactive or not), current smoking status, and alcohol consumption (Astrand, Astrand, Hallbäck, & Kilbom, 1973; Church et al., 2011; Després, 2016; Fleg et al., 2005; Jackson et al., 2009).

At each medical examination, participants' fasting cholesterol, systolic blood pressure, and body fat percentage were assessed and evaluated after a 12-hour overnight fast (Blair et al., 1989). Serum samples were analyzed by automated methods to record total cholesterol for each participant. Systolic blood pressure was measured by the auscultatory method using a mercury sphygmomanometer and body fat percentage was measured using hydrostatic weighing following standardized protocols (Jackson, Lee, & Blair, 1999).

Standardized medical questionnaires were administered at each examination to collect information on participant leisure-time physical activity, smoking status and alcohol consumption. Leisure-time physical activity was self-reported as active or inactive (having no leisure-time physical activity within the last 3 months). Participant smoking status was classified as current smoker or not. Current smokers were considered as such if they smoked presently or had quit within two years of the examination. Alcohol consumption was classified as heavy (>14 units/week for males) or not (Blair et al., 1989).

3.5 Statistical Analysis

Statistical Analysis Software (SAS, version 9.4, Cary, NC) was used for the linear regression and Stata 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.) was used for the quantile regression. The level of statistical significance for all analyses was set to 0.05.

The primary analysis was a linear regression for non-independent data. This analysis allowed for the inference about the mean of CRF. The potential for intra-individual dependence was taken into account via the estimation of applied generalized estimating equations (GEE) with an exchangeable working covariance matrix for the linear regression on the mean (M. Wang, Kong, Li, & Zhang, 2016). Due to potential for non-linearity of age (Fleg et al., 2005), a non-parametric regression was run to determine if linear splines were needed to help assess the association between CRF and age. Based on the results of the non-parametric regression, it was decided that age could be treated as a linear continuous variable in our regression model.

For Model 1, the final adjustment included the covariates age, body fat percentage, resting systolic blood pressure, cholesterol, birth cohort, physical activity, current smoking status, and alcohol consumption. To test our hypothesis that the relationship between CRF and advancing age differs by T2DM status, the interaction between T2DM and age was included in a separate model, Model 2.

Quantile regression assessed the association between cardiorespiratory fitness and T2DM at the adjusted 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 95^{th} percentiles of CRF. The same covariates adjusted for in Model 1 were adjusted for in this quantile regression model. The repeated observations of CRF taken on the same participant may not be independent. The quantile regression estimator is consistent when the data are dependent (Jung, 1996). Since we were interested in population-level, not individual-level, estimates, we estimated the standard errors and confidence intervals with 500 cluster bootstrap samples to account for this potential dependence between observations (Geraci & Bottai, 2006; Lipsitz, Fitzmaurice, Molenberghs, & Zhao, 1997; Liu & Matteo, 2009).

CHAPTER 4

RESULTS

4.1 Exclusion of Observations with Missing Variables

Observations with missing values for body fat percentage, systolic blood pressure, fasting cholesterol, age, smoking status, or alcohol consumption were excluded from the final analysis (n=345), equaling roughly 0.69% of study sample. Excluded observations were compared to those included to assess if missing data was more likely to be associated with the exposure or outcome of interest. Missing observations were not found to be associated with maximal METs ($p = 0.083$) or T2DM status ($p = 0.326$). With the lack of a statistically significant association between inclusion status and exposure or outcome of interest, it was determined that excluding observations with missing variables would not introduce bias to the results. The final sample size was made up of 12,648 participants with 49,704 individual observations (3.63 average visits per participant). In Table 4.1 the baseline characteristics for study participants included in the complete case analysis are presented.

4.2 Interaction

The interaction between T2DM and age was found to be statistically significant (p 0.001). The significance of the interaction term provides evidence that the difference in mean CRF associated with age differs by T2DM status. Figure 4.1 plots the relationship between CRF and age for participants with and without T2DM holding birth cohort, cholesterol, physical activity, systolic BP, body fat percentage, smoking status, and alcohol consumption constant.

4.3 Linear Regression

The estimated coefficients and corresponding confidence intervals (CI) for the predictors of interest from both multiple linear regression models are listed in Table 4.2. In Model 1, a 1-year increment in age was associated with a decrease in CRF by 0.062 METs. Individuals with T2DM saw a 0.124 METs reduction in CRF compared to those without T2DM. For Model 2, the interaction term's statistical significance showed that the difference in mean CRF with advancing age varies by T2DM status. For diabetics, the associated slope for CRF and age is 0.082 METs. For non-diabetics, the associated slope for CRF and age is 0.062 METs. This highlights that the relationship between CRF and advancing age for those with T2DM is associated with an additional decrease of 0.020 METs compared to those without T2DM.

4.4 Quantile Regression

Table 4.3 summarizes the results from the quantile regression estimating percentiles of CRF (0.05, 0.25, 0.5, 0.75, 0.9 and 0.95) assessing the association between CRF, as measured by maximal ACSM METs, and T2DM. Across the 5th, 10th, 25th, 50th, and 75th percentiles of CRF, diabetics had significantly lower CRF (-0.594, -0.456, -0.464, -0.333, -0.207 respectively) compared to non-diabetics. The estimated differences in CRF for the 5th through the 95th percentiles for diabetics (compared to non-diabetics) decreased as the percentiles of CRF increased.

Table 4.1: Baseline characteristics of ACLS population, Dallas, Texas, 1970-2006 (men = 12,648)

	STUDY PARTICIPANTS (N=12648)
	Mean or %
Maximal METs	12.28
Body fat %	20.89
Smoker (yes)	14.45%
Physical Activity (yes)	81.67%
Cholesterol	208.13
Systolic BP	119.94
Age	44.53
COHORT	
Birth Before 1930	13.89%
Birth Year 1931-1940	25.36%
Birth Year 1941-1950	34.27%
Birth After 1950	26.47%
Heavy Drinker (yes)	7.31%

Table 4.2: Effects of predictors at the mean of CRF estimated by generalized estimating equations in men, Dallas, Texas, 1970-2006 (men = 12,648; observations = 49,704)

	Model 1[a]			Model 2[a]		
	COEFFICIENT	**95% CI**	**P VALUE**	**COEFFICIENT**	**95% CI**	**P VALUE**
Intercept	18.817	18.553, 19.085	<.0001	18.816	18.552, 19.079	<.0001
T2DM (yes)	-0.124	-0.219, -0.029	0.0105	0.948	0.312, 1.584	0.0035
Age	-0.062	-0.066, -0.058	<.0001	-0.062	-0.065, -0.058	<.0001
T2DM (yes) * Age	-	-	-	-0.020	-0.032, -0.008	0.0012

[a]Adjusted for body fat percentage, smoking status, cholesterol, physical activity, systolic blood pressure, birth cohort, and alcohol consumption

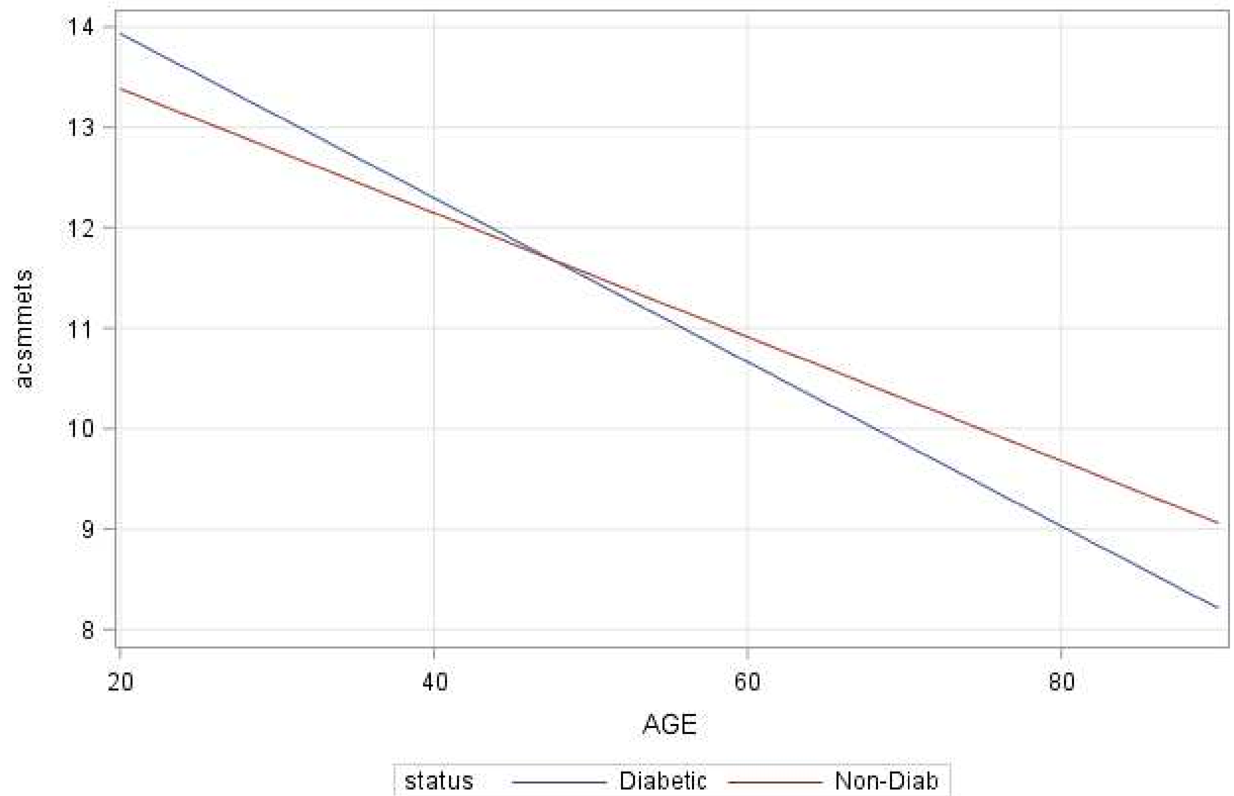
Table 4.3: Regression coefficients of predictors at 7 percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) of the distribution of CRF estimated by quantile regression in men, Dallas, Texas, 1970-2006 (men = 12,648; observations = 49,704)

	REGRESSION COEFFICIENT[a]						
PERCENTILE	**0.05**	**0.1**	**0.25**	**0.5**	**0.75**	**0.9**	**0.95**
T2DM (yes)	-0.594*	-0.456*	-0.464*	-0.333*	-0.207*	-0.140	-0.142
Age	-0.043*	-0.040*	-0.042*	-0.042*	-0.049*	-0.059*	-0.063*

[a]Adjusted for body fat percentage, smoking status, cholesterol, physical activity, systolic blood pressure, birth cohort, and alcohol consumption

*Indicates statistical significance p value<0.05

Figure 4.1: Plot of CRF and age by T2DM status[a] for men, Dallas, Texas, 1970-2006



[a]Adjusted for body fat percentage, physical activity, smoking status, cholesterol, systolic blood pressure, birth cohort, and alcohol consumption

CHAPTER 5

DISCUSSION

5.1 Summary of Results

The purpose of this study was to assess the association of CRF and age by T2DM status. The present study utilized a linear regression analysis and found statistically significant differences in the association between fitness (as measured in ACSM METs) with advancing age among individuals with and without T2DM. An additional quantile regression analysis was conducted and found significant associations between CRF and age and CRF and T2DM status across the entire distribution of CRF.

In our linear regression model including the significant interaction term between T2DM and age, we found that for those with T2DM, the decrease in CRF for each 1-year increment of age was 24.4% higher for diabetics compared to non-diabetics. Our findings are similar to a study conducted by Fleg et. al., that utilized linear mixed-effects regression models and found after a 7.9-year follow-up that there is a longitudinal rate of decline in fitness (as measured by peak VO_2) that is not linear and accelerates as age increases (Fleg et al., 2005). Our study is different from Fleg et. al., in that we compared the decrease in fitness with age between those with and without T2DM. Our findings suggest that the decrease in CRF as individuals age is modified by T2DM status.

As hypothesized, our study found that there was a significant difference in the relationship between CRF and age that varied by T2DM status. We found that there was an additional 0.020 METs decrease in mean CRF for every 1-year increment of age for those with T2DM when compared to those without the disease. Considering that the average maximal METs for those with T2DM was 11.39, this is approximately a 0.72% decrease in mean fitness per every year aged for diabetics (0.49% decrease for non-diabetics). This difference in CRF with advancing age amongst those with and without T2DM is consistent with a finding by Carnethon and colleagues. They showed after adjusting for age, race, smoking status, baseline physical activity, BMI, and treadmill test duration for participants in the CARDIA study, that amongst those who developed T2DM over 20 years, there was a greater decline in fitness when compared to those who did not develop the disease in both men and women (Carnethon et al., 2009). These results are consistent with several other studies that found significant inverse associations between T2DM and fitness (Duck Chul Lee et al., 2009; Sawada et al., 2003; Wei et al., 1999; Zaccardi et al., 2015). The statistical differences in decline of mean CRF with advancing age between those with and without T2DM after adjusting for potential confounders further suggests the importance of looking at this association across the entire distribution of CRF.

When looking at the entire distribution of CRF through quantile regression, the difference in maximal METs between those with and without T2DM decreased as fitness increased (from -0.594 to -0.207). This finding is in line with our original hypothesis. The inverse association between CRF and T2DM was statistically significant at the 5th, 10th, 25th, 50th, and 75th percentiles. For the 90th and 95th percentiles of fitness, the difference in

CRF was not found to be statistically significant. This indicates that there was no evidence of an association between T2DM status and fitness amongst the most fit individuals included in the cohort. Similarly, Lee et al. found in their 2009 study assessing the association between fitness and obesity with T2DM that higher levels of fitness attenuated, but did not completely eliminate the risk of T2DM in obese men compared to unfit obese men (Duck Chul Lee et al., 2009). This finding suggests the importance of maintaining higher levels of fitness to combat the risk of T2DM.

Previous research has shown that the biological mechanisms by which fitness protects against incident T2DM are through several correlated factors such as weight loss, decreases in insulin resistance and improved muscle insulin sensitivity, increased endothelial and autonomic function, and reductions in inflammation and oxidative stress (Carnethon et al., 2009).

In a recent study by Wedell-Neergaard et al, it was found that higher levels of CRF promoted higher levels of health through lower levels of abdominal obesity and lower systematic inflammation (as measured by high-sensitivity C-reactive protein and Interleukin-6) after adjusting for possible confounders. This reduction in systematic inflammation saw an overall reduction in risk for MetSyn, which therefore reduced the risk for T2DM. It has previously been noted that physical activity provides the body with an acute anti-inflammatory response as muscles release IL-6, which further induces the release of IL-10, a major anti-inflammatory cytokine. In the study conducted by Wedell-Neergaard et al, a significant direct relationship between CRF and IL-10 was found. This relationship could indicate that chronic inflammation mediates the relationship between CRF and MetSyn and therefore T2DM (Wedell-Neergaard et al., 2018).

Also, in a recent study by Wang et al., it was determined that a moderate level of muscular strength, as measured by resistance weight machines, was associated with a reduced risk of T2DM, independent of CRF. This indicates that regardless of fitness level, those with T2DM experience a difference in muscular strength compared to those without the disease. The difference in muscular strength could be contributing to those with T2DM fatiguing faster than their non-diabetic counterparts (Y. Wang et al., 2019). Future studies examining the relationship between CRF and age, by T2DM status after controlling for muscular strength should be done to further explore the relationship between CRF as individuals age.

The findings from Wedell-Neergaard et al. and Wang et al. further emphasize the importance of maintaining higher levels of CRF to combat against the risk of T2DM. As suggested by the American Heart Association's recent statement on the importance of assessing CRF, through frequent and habitual physical activity focusing on increasing endurance, CRF is likely to increase resulting in the potential reduction in risk for T2DM, cardiovascular events, and even mortality (Ross et al., 2016).

5.2 Comparing Quantile and Linear Regression Models

Looking at Model 1, the coefficient for diabetics (compared to non-diabetics) was -0.124. This equates to a decrease in mean CRF for those with T2DM of 0.124 maximal METs when comparing those without T2DM. However, when assessing the association between T2DM across the entire distribution of CRF via quantile regression, much larger magnitudes of decreases in CRF were found to be significant (from -0.594 to -0.207 METs). These differences suggest the inadequacy of assessing associations about the mean of fitness via linear regression. Employing linear regression greatly underestimated the association between T2DM and CRF across the lower percentiles of fitness.

Although it was not the aim of this project to examine the effect of age on CRF using quantile regression, further exploration of the results highlights the benefits of quantile regression over linear regression. For example, Model 1 for the linear regression analysis, a 1-year increase in age is associated with a 0.062-MET reduction in CRF. However, the quantile regression conveys a slightly different picture of the association between age and CRF. For each adjusted percentile of CRF (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th}), a 1-year increase in age is associated with a significant reduction in METs. For the 5^{th}, 10^{th}, 25^{th}, and 50^{th} percentiles, a 1-year increase in age is associated with a reduction in CRF ranging from -0.040 to -0.043 METs. This relationship saw even larger reductions in CRF among the 75^{th}, 90^{th}, and 95^{th} percentiles (-0.049, -0.059, -0.063 METs respectively). Previous studies have found that the rate of decline of fitness with increase in age is not linear and accelerates with advancing age, regardless of habitual high-intensity physical activity (Fleg et al., 2005). Since the interaction between age and T2DM status was significant in the linear regression, assessing the interaction between age and T2DM on CRF in the quantile regression analysis would have allowed us to better define the relationship between T2DM and CRF with advancing age.

5.3 Public Health Significance

It is important to note that the relationships between the covariates across the percentiles of CRF could not have been captured by linear regression alone. The use of quantile regression allowed for a much more in-depth look at the relationships between the covariates and CRF, which allows for greater understanding of the full picture. This analysis allowed us to determine that the association of T2DM and fitness was greater at the lower percentiles of CRF than at the higher percentiles of CRF. The importance of utilizing quantile regression has been demonstrated in previous studies as well. Bottai et. al. (2014) found that the relationship between physical activity and BMI was "not uniform across the distribution of BMI." He argues that the analytic approach provided by quantile regression should be used in any study where the effects of the covariates could differ across the distribution of the outcome variable. Finding significant differences in T2DM and age across the distribution of CRF further support the importance of utilizing quantile regression to assess relationships between independent variables and outcomes of interest, especially where the association could vary at differing levels of the outcome.

The findings presented in this study have the potential to influence the prescription of fitness for individuals looking to reduce their risk of adverse health outcomes. For example, at the 5th percentile for CRF, the estimated decrease in CRF for diabetics (compared to non-diabetics) was -0.594 METs. Although 0.594 METs does not equate to much in terms of energy expenditure, it does indicate a difference between the two populations. This difference should be taken into consideration when prescribing exercise and fitness regimens, especially for those beginning physical activity with lower levels of physical fitness. Functional capacity for exercise has been classified based on maximal METs by Jette and colleagues (Jetté, Sidney, & Blümchen, 1990). Exercise prescriptions can be tailored to the patient based on their classification of functional capacity for METs. Depending on where the patient falls in the classification, a difference of 0.594 METs might alter the prescription of fitness and could result in prescribing activities that may not be suitable for the individual to perform. Although CRF has been found to be a significant indicator of risk in T2DM and mortality (Katzmarzyk et al., 2007; Kokkinos, 2012), it is currently not implemented as a measurement in clinical practice. The American Heart Association has called for the inclusion of the measurement of CRF in routine medical practices for all adults (Ross et al., 2016). The findings from this study further emphasize that point and show that advocating for the routine assessment of CRF should be a primary concern for public health professionals.

Looking across the entire distribution of CRF has allowed us to determine the relationship between T2DM and fitness at both the lower and upper tails of the distribution. In this study, at the 75th percentile for CRF, the estimated decrease in CRF for diabetics (compared to non-diabetics) was only -0.207 METs. This shows at the higher levels of CRF in our population holding age, cholesterol, systolic BP, birth cohort, body fat percentage, physical activity, current smoking status, and alcohol consumption constant, there was minimal difference in fitness between those with and without T2DM. As the percentiles of CRF increased to the 90th and 95th percentile, the difference became insignificant.

It has been noted in a pooled analysis of studies that a 1-MET increase in CRF is associated with a 10%-25% improvement in survival. Focusing exercise as a means to increase CRF should become a standard of practice as CRF is responsive to therapy and increasing CRF is associated with decreases in adverse health and clinical outcomes(Ross et al., 2016).

5.4 Strengths and Weaknesses

The findings presented in this study are not without limitations. First, the participants included in the study were individuals from the ACLS, a study comprised of mainly Non-Hispanic white men who are of higher socioeconomic and educational status (Blair et al., 1989). These individuals may be a more health conscious subsample of the entire population and therefore may be less likely to be associated with the predictor of interest, T2DM. Because of this, it is safe to assume that the present findings might be an underestimate of the true difference in CRF between those with T2DM and those without. Although the lack of diversity in the cohort may limit the generalizability of the findings, it would not affect the internal validity of the study. Additionally, there is potential for misclassification bias on the exposure of interest, T2DM. Individuals were categorized as diabetic if they self-reported as being diagnosed by a physician or if they presented with a fasting plasma glucose level of >126 mg/dL. Those with baseline T2DM were not included in the study. Due to the analysis using repeated measures observations, those who became diabetic and were classified as diabetic in later visits were classified in earlier visits as non-diabetic. Since T2DM is a disease that develops over time (Fonseca, 2009), it is likely that some individuals were classified as non-diabetic, but were likely pre-diabetic or experiencing symptoms of MetSyn. This classification could lead to differences in CRF between those with and without T2DM being biased towards the null.

One of the major strengths of this study is the quantile regression analysis taking into account the entire distribution of the outcome of interest, CRF. To our knowledge, this is the first study utilizing quantile regression focusing on fitness as the outcome. The study also is strengthened by a large number of participants having several extensive medical examination visits across a relatively long follow-up (12,639 participants with average of 3.63 visits across 36 years). The objective measurement of fitness through maximal METs as determined by treadmill tests is also considered a strength for this study.

5.5 Recommendations for Future Research

In conclusion, the present study found that the relationship between fitness and age varies by T2DM status. As diabetics age, their CRF levels decrease at a faster rate when compared to those without T2DM. This study also employed quantile regression and found that there was a significant inverse relationship between T2DM and CRF that decreases in magnitude as the percentiles of CRF increased. Additional research, with a larger more diverse sample size, will help to further quantify the association between T2DM and CRF and help to establish tailored interventions for populations based on their T2DM status that focuses on the individual's fitness level. Furthermore, future studies should assess the relationship between their predictor and outcomes of interest with quantile regression to understand the impact of that predictor across the entire distribution of the outcome.

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