Low Cardiorespiratory Fitness Is Associated with Markers of Insulin Resistance in Young, Normal Weight, Hispanic Women

Chantal A. Vella, PhD,¹ Gary P. Van Guilder, PhD,² and Lance C. Dalleck, PhD³

Abstract

Background: Low cardiorespiratory fitness (CRF) and its decline over time are predictors of the development of diabetes in black and Caucasian women, independent of obesity. It is unclear, however, if the adverse effect of low CRF on the risk of diabetes in Hispanic women is mediated by obesity. Our purpose was to determine the associations of CRF with markers of insulin resistance in 68 normal weight Hispanic women.

Methods: Obesity indicators included body mass index (BMI), body composition by DXA, and waist circumference. CRF was measured by indirect calorimetry. A glucose tolerance test was used to measure markers of insulin resistance: homeostasis model assessment, fasting insulin, 2-hr insulin, area under the curve insulin, qualitative insulin sensitivity check, and insulin sensitivity index. Pearson correlation and multiple regression analyses were used to identify associations between CRF and markers of insulin resistance. Multivariate ANOVA was used to compare markers of insulin resistance over quartiles of CRF.

Results: Low CRF was significantly associated with all markers of insulin resistance ($P < 0.01$). These associations were independent of age, BMI, waist circumference, family history of T2DM, and triglycerides (CRF standardized beta range: -0.27 to -0.46 , $P < 0.05$). However, these associations were attenuated when body composition, specifically fat-free mass, was entered into the model (CRF standardized beta range: -0.03 to 0.21 , $P > 0.05$). All markers of insulin resistance improved linearly across CRF quartiles ($P < 0.05$).

Conclusions: Our findings suggest that low CRF may be an important predictor of diabetes risk in Hispanic women and that fat-free mass rather than overall body adiposity mediates these relationships.

Introduction

IN THE PAST 25 YEARS, the annual number of newly diagnosed cases of type 2 diabetes among US adults has tripled.¹ A major disparity in these data is that while rates of diabetes have been relatively stable during this time for the non-Hispanic white population, it disproportionately affects a greater number of Hispanics.² In fact, recent epidemiological data indicate that in contrast to non-Hispanic whites the age-adjusted percentage of adults with diabetes is nearly twice as high in Hispanics, new cases of type 2 diabetes have quadrupled in younger subgroups of the Hispanic population, and rates of new diabetes increased the most (65%) in Mexican/Mexican American women from 1997 to 2011.¹

What is more troubling is the onset of risk factors that accelerate diabetes progression, particularly impaired glu-

cose tolerance and insulin resistance (*i.e.*, prediabetes) occur at younger ages in Hispanics,³ contributing to an especially higher risk of early diabetic health consequences. This is exemplified by an increased prevalence of serious diabetes-related complications (*i.e.*, heart disease and stroke, blindness, kidney failure, and lower limb amputation) and mortality compared to white Americans.² Hispanic women in particular have a higher prevalence of obesity and metabolic syndrome,⁴ worse insulin sensitivity,⁵ and a greater burden of major cardiometabolic risk factors,^{6,7} all of which are central to their accelerated risk of diabetes.³

Physical inactivity and poor cardiorespiratory fitness (CRF) account for 8.3% of premature deaths attributable to diabetes in the United States every year,⁸ and the impact of this public health problem is worse in Mexican Americans who are generally less physically active and less fit than

¹Department of Movement Sciences, University of Idaho, Moscow, Idaho.

²Department of Health and Nutritional Sciences, South Dakota State University, Brookings, South Dakota.

³Recreation, Exercise, and Sport Science Department, Western State Colorado University, Gunnison, Colorado.

non-Hispanic whites.⁹ Indeed, while results from the CARDIA study¹⁰ demonstrated that poor CRF and its decline over 7 years of follow-up were independent predictors of the development of diabetes in young African American and Caucasian women, these findings have not been corroborated in young Hispanic women. Moreover, it is also not clear if the adverse effect of low CRF on the risk of diabetes in Hispanic women is mediated by total body adiposity, which has been shown to attenuate the relationship in other ethnic groups. Experimentally, prior studies have relied on indirect estimates of CRF^{10–13} and total body adiposity,^{10–13} and these data can only be applied to women of African American and Caucasian descent.

Nevertheless, it is well established from many prospective cohort studies that higher CRF lowers the risk of diabetes and protects from the adverse impacts of the disease on all-cause and CVD mortality, in part through improved insulin sensitivity and glucose tolerance.^{14,15} Understanding the relationships between low CRF and markers of insulin resistance in young women of Hispanic origin is of growing importance to eliminate the health disparities responsible for the premature development of diabetes in this ethnic minority.

Therefore, the purpose of the present study was to determine the association of CRF with markers of insulin resistance in young, normal weight, Hispanic women. We hypothesized that lower CRF would be independently and inversely associated with markers of insulin resistance and that these associations would be independent of total body adiposity.

Materials and Methods

Sixty-eight young normal weight women of Mexican descent, aged 20–39 years, participated in the study. Normal weight was defined as a body mass index (BMI) of 18.5–24.9 kg·m⁻².¹⁶ Participants were tested during the follicular phase of their menstrual cycle as determined by self-report (within 10 days of the start of menstruation). Participants were excluded if they had any of the following: currently taking antihypertensive or lipid-lowering medications; current pregnancy; diagnosed cardiovascular, metabolic, or pulmonary disease; irregular menstrual cycles; current smoker; or unable to perform exercise testing. The study was approved by the University of Idaho Institutional Review Board.

After reading and signing the consent, each participant was invited to the laboratory on two occasions for a series of testing. For the first visit, participants were instructed to report to the laboratory after a 12-hr fast and abstain from exercise for 48 hr. During this visit, testing included anthropometric and blood pressure measurements and a 2-hr oral glucose tolerance test (OGTT). The second visit included body composition and CRF testing.

Height was recorded using a wall-mounted stadiometer, and body weight was obtained using a calibrated digital scale. Normal weight was defined as a BMI of 18.5–24.9 kg·m⁻².¹⁶ After 5 min of seated rest, two readings of blood pressure within 5 mmHg were averaged.¹⁷ Body composition was measured by DXA (Lunar DPX-NT; GE Lunar Corp., Madison, WI) following the standard protocol.

For the OGTT, a catheter was placed into an antecubital vein, and blood samples were collected at baseline (0), 30, 60, 90, and 120 min. Participants were then given an oral standard load of 75 g glucose and asked to consume the entire drink within 5 min. Frozen serum samples were sent to the University of Alabama Center for Clinical and

Translational Sciences (CCTS) for analysis. Glucose was measured by the glucose oxidase method (Sirus Clinical Chemistry Analyzer; Stanbio Laboratory, Boerne, TX). Insulin was measured using an immunoenzymatic method (TOSOH AIA-600 II Analyzer; TOSOH Bioscience, South San Francisco, CA). This assay had a minimum sensitivity of 1.0 µU/mL, interassay coefficient of variation (CV) of 4.42%, and intra-assay CV of 1.49%. HDL-C was measured using the colorimetric method with a two-reagent system (Sirus Clinical Chemistry Analyzer; Stanbio Laboratory, Boerne, TX). The assay had a minimum sensitivity of 0.13 mM and an interassay CV of 5.30%. Triglycerides were assessed with the glycerolphosphate (GPO) colorimetric method (Sirus Clinical Chemistry Analyzer; Stanbio Laboratory, Boerne, TX), with a minimum sensitivity of 0.06 mM and an interassay CV of 4.28%.

Six estimates of insulin resistance were used in the study: fasting insulin, 2-hr insulin, the homeostasis model assessment of insulin resistance (HOMA), area under the curve (AUC) insulin, the quantitative insulin sensitivity check index (QUICKI), and the composite insulin sensitivity index (ISI). These estimates have been shown to correlate well with the more direct measures of insulin sensitivity, such as the hyperinsulinemic–euglycemic clamp.^{18,19} HOMA was calculated as fasting insulin (µU/mL) times fasting glucose (mM) divided by 22.5; QUICKI was calculated as 1 divided by log fasting insulin (µU/mL) plus log fasting glucose mg/dL; AUC insulin was calculated using the trapezium rule,²⁰ and ISI was calculated as previously described.¹⁹

Peak oxygen consumption (VO_{2peak}) was determined using a continuous exercise test on a treadmill (Track Master X425C; Full Vision, Inc., Newton, KS). After measuring resting expired gases for 2 min, a 2-min warm-up was performed at 94.0 m/min. The treadmill speed was then increased to a comfortable jogging pace as determined by the participant for 2 min (147.5–174.0 m/min). The treadmill grade was then increased by one percent each minute thereafter until volitional fatigue.

During the exercise test, oxygen consumption (VO₂), carbon dioxide production, ventilation, heart rate, and respiratory rate were measured using a computerized metabolic system (Parvo Medics' TrueOne[®] 2400, Salt Lake City, UT). Heart rate was continuously recorded using a heart rate monitor and receiver integrated with the metabolic cart (Polar Electro, Inc., Lake Success, NY). For all VO₂ analyses, data were smoothed with a 15-breath moving average.²¹ Peak oxygen consumption was recorded as the highest VO₂ obtained during the last minute of exercise. Participants were subsequently categorized into VO_{2peak} quartiles: quartile 1: 1.48–1.91 L/min (*n*=17), quartile 2: 1.92–2.20 L/min (*n*=19), quartile 3: 2.21–2.54 L/min (*n*=16), and quartile 4: 2.55–2.86 L/min (*n*=16), which allowed for a similar distribution across groups.

Sample size estimates and statistical analyses

A priori sample size estimates were generated using GPower 3.1.9.2. Using linear multiple regression sample size calculations and estimating a small effect size (0.15) with three predictor variables, 62 subjects would result in a power of 0.80 and α of 0.05.

Data were analyzed for normality and homogeneity of variance. Variables that were not normally distributed were

log transformed (HOMA, fasting insulin, AUC insulin, and triglycerides). All analyses were performed using relative (correcting for body weight statistically) and absolute $\text{VO}_{2\text{peak}}$. The outcomes were similar, and thus, we have reported all data using absolute $\text{VO}_{2\text{peak}}$ (L/min).

Pearson product-moment correlation analyses were used to establish simple associations among variables. Multivariate linear regression analyses were used to establish the independent contributions of CRF on each marker of insulin resistance. Several regression models were tested and included body weight, BMI, body composition, waist circumference, age, family history of type 2 diabetes, and triglycerides as covariates. Fasting glucose was not used as a covariate in the regression models because it was used to calculate three of the indices of insulin resistance. Results from the regression models, including age, BMI, family history of type 2 diabetes, triglycerides, and body composition, are presented because these variables contributed more to explained variance (R^2) compared with models that included waist circumference and body weight. Furthermore, regression diagnostics were performed and indicated that there were no problems with multicollinearity among independent variables in the final models (*e.g.*, tolerance, condition index, and variance inflation factor). Multivariate ANOVA was used to compare demographic variables and markers of insulin resistance among quartiles of CRF. All analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL). A value of $P < 0.05$ was accepted as the minimal level of significance.

Results

Participant characteristics are presented in Table 1. Although all participants were classified as normal weight based on BMI, average percentage body fat was 32%, with a range of 21%–45%. Participants had fair fitness levels, with mean relative $\text{VO}_{2\text{peak}}$ (38.7 ± 5.4 mL/kg/min) falling in the

55th percentile for young women.²² Forty-five participants (66%) had a positive family history of type 2 diabetes, and depending on the guidelines used, three (4%) and 20 (29%) had a waist circumference considered to be high risk (≥ 88 cm and ≥ 80 cm, respectively).^{23,24}

There was a significant main effect of CRF quartile for body weight ($P < 0.001$), fat-free mass ($P < 0.001$), relative and absolute $\text{VO}_{2\text{peak}}$ ($P < 0.001$), fasting insulin ($P = 0.004$), 2-hr insulin ($P = 0.011$), HOMA ($P = 0.004$), QUICKI ($P = 0.001$), and ISI ($P = 0.009$; Table 1 and Figure 1). Body weight, fat-free mass, relative $\text{VO}_{2\text{peak}}$, QUICKI, and ISI increased linearly across CRF quartiles ($P < 0.01$ for trend), whereas body fat percentage, triglycerides, fasting insulin, 2-hr insulin, HOMA, and AUC insulin decreased across CRF quartiles ($P < 0.01$ for trend). On average, women in the highest two quartiles of CRF had healthier metabolic profiles than those in the lowest two quartiles of CRF.

CRF and fat-free mass were significantly associated with all markers of insulin resistance (Table 2). Triglycerides were significantly related to all markers of insulin resistance except AUC insulin. Body weight and waist circumference were significantly and negatively associated with 2-hr insulin and AUC insulin, respectively. These associations were opposite of what was expected but may be due to the normal BMI of the sample. BMI, HDL, and fat mass were not associated with any of the markers of insulin resistance in this cohort. Explained variance from significant correlations ranged from 9% to 24%, indicating a low to moderate level of explained variance. CRF explained 9%–15% of the variance; triglycerides explained 11%–22% of the variance, whereas fat-free mass explained 14%–24% of the variance in markers of insulin resistance.

The contribution of CRF to markers of insulin resistance was independent of age, BMI, waist circumference, family history of type 2 diabetes, and triglycerides ($P < 0.05$) but was not independent of body composition ($P > 0.05$, Table 3).

TABLE 1. PARTICIPANT CHARACTERISTICS

Variable	Fitness quartile 1 (<i>n</i> = 17)	Fitness quartile 2 (<i>n</i> = 19)	Fitness quartile 3 (<i>n</i> = 16)	Fitness quartile 4 (<i>n</i> = 16)	All (<i>N</i> = 68)
Demographics					
Age (years)	25.8 ± 5.9	24.6 ± 5.1	26.1 ± 3.7	25.0 ± 4.3	25.3 ± 4.8
Body weight (kg)*§	53.5 ± 4.2	57.2 ± 5.6	57.8 ± 4.0 ^a	61.6 ± 4.1 ^{ab}	57.5 ± 5.3
Body mass index (kg/m ²)	21.9 ± 1.5	22.0 ± 1.8	22.3 ± 1.5	22.7 ± 1.4	22.2 ± 1.6
Fat (%)§	34.3 ± 4.5	32.8 ± 7.1	30.4 ± 5.4	29.9 ± 5.6	31.9 ± 5.9
Fat (kg)	18.5 ± 3.4	19.1 ± 5.6	17.7 ± 4.1	18.5 ± 4.4	18.5 ± 4.4
Fat-free mass (kg)*§	35.0 ± 2.3	38.1 ± 2.2 ^a	40.1 ± 2.5 ^a	43.1 ± 3.0 ^{abc}	39.0 ± 3.8
Peak oxygen consumption (mL/kg/min)*§	33.1 ± 3.7 ^{bcd}	36.9 ± 3.8 ^{acd}	41.7 ± 3.9 ^{abd}	43.8 ± 3.0 ^{abc}	38.7 ± 5.4
Peak oxygen consumption (L/min)*§	1.8 ± 0.1	2.1 ± 0.1	2.4 ± 0.1	2.7 ± 0.1	2.2 ± 0.4
Cardiovascular disease risk factors					
Waist circumference (cm)	75.3 ± 5.4	76.2 ± 6.7	76.1 ± 6.5	78.7 ± 5.2	76.5 ± 6.0
Fasting glucose (mmol/L)	5.0 ± 0.2	5.1 ± 0.4	4.8 ± 0.2	5.0 ± 0.4	5.0 ± 0.3
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.5 ± 0.4	1.6 ± 0.5	1.5 ± 0.3	1.5 ± 0.4
Triglycerides (mmol/L)§	1.0 ± 0.4	0.8 ± 0.4	0.8 ± 0.3	0.7 ± 0.3	0.8 ± 0.4
Systolic blood pressure (mmHg)*	106.0 ± 7.5	107.5 ± 8.7	100.0 ± 6.1 ^{bd}	108.6 ± 9.8	106.0 ± 8.6
Diastolic blood pressure (mmHg)*	70.7 ± 5.6	70.2 ± 7.4	64.6 ± 4.3 ^{ab}	68.8 ± 6.0	69.0 ± 6.3

* $P < 0.05$ for main effect of $\text{VO}_{2\text{peak}}$ quartile.

§ $P < 0.05$ for linear trend across $\text{VO}_{2\text{peak}}$ quartiles.

^aDifferent than quartile 1.

^bDifferent than quartile 2.

^cDifferent than quartile 3.

^dDifferent than quartile 4.

FIG. 1. Markers of insulin resistance across VO_{2peak} quartiles. $P < 0.01$ for main effect of VO_{2peak} quartile on fasting insulin, 2-hr insulin, HOMA, QUICKI, and ISI. $P < 0.01$ for linear trend across all indices of insulin resistance. ^aDifferent than quartile 1; ^bdifferent than quartile 2. HOMA, homeostasis model assessment of insulin resistance; AUC, area under the curve; QUICKI, quantitative insulin sensitivity check index; ISI, insulin sensitivity index; VO_{2peak} , peak oxygen consumption.

Across all models, fat-free mass was a stronger covariate compared with fat mass.

Discussion

The primary new findings of the present study are that in a healthy sample of young, normal weight, Hispanic women,

low CRF was inversely associated with markers of insulin resistance, and these relationships were independent of total body adiposity as determined by BMI and abdominal obesity as estimated by waist circumference. However, these associations appeared to be contingent on more precise assessments of body composition from DXA scanning. This notion is supported by the finding that fat-free mass rather

TABLE 2. PEARSON CORRELATIONS

	<i>Fasting insulin</i>	<i>2-hr insulin</i>	<i>HOMA</i>	<i>AUC insulin</i>	<i>QUICKI</i>	<i>ISI</i>
VO ₂ peak	−0.348 ^a	−0.392 ^a	−0.346 ^a	−0.302 ^b	0.354 ^a	0.364 ^a
Body weight	−0.162	−0.245 ^b	−0.127	−0.197	0.121	0.216
BMI	−0.011	0.015	−0.011	−0.018	−0.006	0.013
Fat mass	0.132	0.127	0.166	0.125	−0.153	−0.101
Fat-free mass	−0.386 ^a	−0.491 ^a	−0.376 ^a	−0.425 ^a	0.358 ^a	0.436 ^a
Waist	−0.159	−0.141	−0.153	−0.245 ^b	0.174	0.288 ^b
Age	−0.185	−0.195	−0.173	−0.253 ^b	0.161	0.230
TG	0.461 ^a	0.335 ^a	0.467 ^a	0.217	−0.472 ^a	−0.411 ^a
HDL	−0.206	−0.186	−0.215	−0.018	0.223	0.117
LDL	0.223	0.041	−0.215	−0.018	−0.213	0.261 ^b
Glucose	0.336 ^a	0.086	0.470 ^a	0.087	−0.475 ^a	−0.379

^a*P* < 0.01.^b*P* < 0.05.

HOMA, homeostasis model assessment of insulin resistance; AUC, area under the curve; QUICKI, quantitative insulin sensitivity check index; ISI, insulin sensitivity index; VO₂peak, peak oxygen consumption; BMI, body mass index; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

than total body fat mass mediated the relationship between low CRF and markers of insulin resistance in Hispanic women. Collectively, these novel findings suggest that poor CRF in young, normal weight, Hispanic women is an important clinical marker for identifying individuals who may have a premature increased risk for developing diabetes later in life. Lifestyle intervention strategies that promote physical activity and improvements in CRF while also maintaining and/or increasing skeletal muscle mass may preserve cardiometabolic health and insulin sensitivity in this population.

In the past decade, low CRF, which is a feature of the metabolic syndrome²⁵ and tightly associated with the car-

diometabolic abnormalities that often accompany obesity,²⁶ has been shown to be an independent predictor of early mortality from all-cause and cardiovascular diseases. For example, Aspenes et al.²⁷ reported that each 5 mL/kg/min decrement in VO₂peak corresponded to an ~56% higher prevalence of CVD risk factor clustering in Norwegian men and women. Similarly, Erez et al.¹² reported that low CRF was associated with a high burden of cardiovascular disease risk factors, including impaired fasting glucose, in middle-aged men and women. Carnethon et al.¹¹ reported that baseline fitness in young adults was inversely related to the risk of developing hypertension, diabetes, metabolic syndrome,

TABLE 3. MULTIPLE LINEAR REGRESSION ANALYSES TO EXAMINE THE INDEPENDENT CONTRIBUTION OF CRF ON MARKERS OF INSULIN RESISTANCE AFTER ADJUSTMENT FOR COVARIATES

<i>Dependent variable</i>	<i>Independent variable</i>	<i>B ± SEE</i>	<i>Standardized beta</i>	<i>P</i>
Fasting insulin				
Model 1 <i>R</i> ² = 0.190	VO ₂ peak	−0.189 ± 0.058	−0.385	0.002
Model 2 <i>R</i> ² = 0.290	VO ₂ peak	−0.134 ± 0.058	−0.272	0.023
Model 3 <i>R</i> ² = 0.153	VO ₂ peak	−0.087 ± 0.089	−0.176	0.335
2-hr insulin				
Model 1 <i>R</i> ² = 0.249	VO ₂ peak	−33.679 ± 8.250	−0.461	<0.001
Model 2 <i>R</i> ² = 0.300	VO ₂ peak	−27.836 ± 8.489	−0.381	0.002
Model 3 <i>R</i> ² = 0.248	VO ₂ peak	−2.572 ± 12.489	−0.035	0.838
HOMA				
Model 1 <i>R</i> ² = 0.191	VO ₂ peak	−0.202 ± 0.062	−0.384	0.002
Model 2 <i>R</i> ² = 0.288	VO ₂ peak	−0.144 ± 0.062	−0.274	0.023
Model 3 <i>R</i> ² = 0.158	VO ₂ peak	−0.098 ± 0.095	−0.186	0.307
AUC insulin				
Model 1 <i>R</i> ² = 0.206	VO ₂ peak	−0.194 ± 0.062	−0.366	0.002
Model 2 <i>R</i> ² = 0.216	VO ₂ peak	−0.176 ± 0.065	−0.332	0.009
Model 3 <i>R</i> ² = 0.176	VO ₂ peak	0.017 ± 0.095	0.032	0.859
QUICKI				
Model 1 <i>R</i> ² = 0.188	VO ₂ peak	0.029 ± 0.009	0.387	0.002
Model 2 <i>R</i> ² = 0.286	VO ₂ peak	0.021 ± 0.009	0.276	0.022
Model 3 <i>R</i> ² = 0.155	VO ₂ peak	0.016 ± 0.014	0.211	0.250
ISI				
Model 1 <i>R</i> ² = 0.233	VO ₂ peak	2.956 ± 0.841	0.401	0.001
Model 2 <i>R</i> ² = 0.297	VO ₂ peak	2.294 ± 0.858	0.311	0.010
Model 3 <i>R</i> ² = 0.221	VO ₂ peak	0.562 ± 1.306	0.076	0.668

Model 1 adjusted for age, BMI, and family history of T2DM; model 2 adjusted for age, BMI, family history of T2DM, and triglycerides; model 3 adjusted for fat and fat-free mass.

and hypercholesterolemia in middle age. Moreover, in 53,785 middle-aged men and women of the Aerobics Center Longitudinal Study of physical activity and fitness on cardiometabolic health outcomes, Blair²⁸ estimated that low CRF accounts for more deaths than obesity, smoking, hypertension, high cholesterol, and diabetes. Nevertheless, few studies have determined the associations between low CRF and markers of insulin resistance, and none have identified these associations in nonobese Hispanic women.

The results of the current study, in which lower CRF was associated with a higher degree of insulin resistance in young Hispanic women, represent an important extension of this literature. Our results indicate that as CRF increases from the first to the fourth quartile, markers of insulin resistance improve in a linear manner. This significant linear trend, which was evident with each of the six markers of insulin resistance, is of emerging importance because the prevalence of type 2 diabetes affects Hispanics disproportionately than other ethnicities.⁵ For instance, in the United States, the risk of diagnosed diabetes is 87%²⁹ higher in Mexican Americans than in non-Hispanic whites.

Our data also suggest that overall, women in higher CRF quartiles demonstrated more favorable cardiometabolic profiles than those in the lower CRF quartiles, suggesting that increases in fitness may preserve cardiometabolic health and insulin sensitivity. In fact, we recently reported in our community-based exercise program³⁰ that adults who demonstrated the greatest improvement in CRF (*i.e.*, 20% or more) were significantly more likely to eliminate components of the metabolic syndrome. Adults who reversed their metabolic abnormalities demonstrated a 1-MET increase in fitness. In light of recent data reporting that a 1-MET increase in fitness reduces CVD mortality by 18%,³¹ the findings of the present study point to a need to determine CRF in young Hispanics without known CVD in whom intensive primordial and primary prevention strategies are warranted.

It is important to note that poor CRF is recognized to be an important underlying feature of those with increased cardiometabolic risk despite normal BMI and overall adiposity—a subset of nonobese people (often referred to as “metabolically obese but normal weight”) who present with insulin resistance, hypertriglyceridemia, and premature coronary heart disease.³² In the present study, Hispanic women presented with a high degree of body fat relative to their total body weight and a healthy BMI. These data suggest that, despite being normal weight and without abdominal obesity, low CRF may underlie an increased risk of type 2 diabetes and cardiovascular disease later in life in this young ethnic minority of apparently healthy women. Identifying young women with low CRF may reveal more Hispanics at risk for an earlier onset of insulin resistance that might otherwise go unnoticed.

In contrast to previous findings,^{10,11} our data indicated that the associations between low CRF and markers of insulin resistance were independent of BMI and waist circumference. Unlike other studies, our sample was normal weight based on BMI, and few participants had a waist circumference above the risk factor threshold, which may explain why these factors did not mediate the relationships between low CRF and markers of insulin resistance. However, we demonstrated a marked attenuation in the association of low CRF with markers of insulin resistance when we statistically adjusted for body composition as measured by DXA. For every model, fat-free mass mediated the re-

lationship between VO₂peak and markers of insulin resistance. It is well accepted that skeletal muscle is the predominant site of insulin resistance in type 2 diabetes. CRF, gained through physical activity, may promote insulin sensitivity in several ways, including increasing skeletal muscle (a) insulin signaling kinetics, (b) enzymes related to glucose metabolism, (c) myoglobin content, (d) oxidative capacity, and (e) capillary density and blood flow.³³

This study has several strengths, including accurate and reliable measures of CRF and body composition by indirect calorimetry and DXA, respectively, and a comprehensive assessment of insulin sensitivity in an understudied yet growing segment of the US minority population living along the Texas–Mexico border. We recognize that the participants were a convenience sample of volunteers of Mexican origin living along the Texas–Mexico border, which may limit the generalizability of the findings to other Hispanic populations in nonborder regions of the United States.

In conclusion, we are the first to show that low CRF is significantly and independently associated with markers of insulin resistance in a young subgroup of nonobese Hispanic women. These findings suggest that low CRF may be an important predictor of type 2 diabetes risk in Hispanic women and that fat-free mass rather than overall body adiposity mediates these relationships. Our findings in addition to others^{10,11,27} demonstrate the importance of low CRF in young adults as a modifiable risk factor for cardiometabolic health. Further research is needed to investigate whether change in fitness over time is predictive of incident diabetes in Hispanic samples.

Acknowledgments

This study was supported by the NIH NIDDK 1SC2DK083061. The authors would like to thank all the participants who took part in this study and the University of Texas El Paso research team who helped with recruitment and data collection.

Author Disclosure Statement

No competing financial interests exist.

References

1. Centers for Disease Control and Prevention, National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014, Atlanta, GA: US Department of Health and Human Services; 2014.
2. Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. *Ann Intern Med* 1996;125:221–232.
3. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the US Population: National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care* 2006;29:1263–1268.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third national health and nutrition examination survey. *JAMA* 2002; 287:356–359.
5. Ho RC, Davy KP, Hickey MS, et al. Behavioral, metabolic, and molecular correlates of lower insulin sensitivity in Mexican-Americans. *Am J Physiol Endocrinol Metab* 2002; 283:E799–E808.
6. St-Onge MP, Janssen I, Heymsfield SB. Metabolic syndrome in normal-weight Americans: New definition of the

- metabolically obese, normal-weight individual. *Diabetes Care* 2004;27:2222–2228.
7. Winkleby MA, Kraemer HC, Ahn DK, et al. Ethnic and socioeconomic differences in cardiovascular disease risk factors: Findings for women from the third National Health and Nutrition Examination Survey, 1988–1994. *JAMA* 1998;280:356–362.
 8. Lee IM, Shiroma EJ, Lobelo F, et al. Lancet Physical Activity Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. *Lancet* 2012;380:219–229.
 9. Carnethon MR, Gulati M, Greenland P. Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. *JAMA* 2005;294:2981–2988.
 10. Carnethon MR, Sternfeld B, Schreiner PJ, et al. Association of 20-year changes in cardiorespiratory fitness with incident type 2 diabetes. *Diabetes Care* 2009;32:1284–1288.
 11. Carnethon MR, Gidding SS, Nehgme R, et al. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* 2003;290:3092–3100.
 12. Erez A, Kivity S, Berkovitch A, et al. The association between cardiorespiratory fitness and cardiovascular risk may be modulated by known cardiovascular disease risk factors. *Am Heart J* 2015;169:915–923.
 13. Wei M, Gibbons LW, Mitchell TL, et al. The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 1999;130:89–96.
 14. Mora S, Cook N, Buring JE, et al. Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. *Circulation* 2007;116:2110–2118.
 15. Lee S, Kuk JL, Katzmarzyk PT, et al. Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men. *Diabetes Care* 2005;28:895–901.
 16. National Heart Lung Blood Institute, Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD, National Heart Lung and Blood Institute, 1998. Report 98–4083.
 17. National Heart, Lung, and Blood Institute. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Institutes of Health, 1997. Report number 98–4080.
 18. Malita FM, Karelis AD, St-Pierre DH, et al. Surrogate indexes vs. euglycaemic-hyperinsulinemic clamp as an indicator of insulin resistance and cardiovascular risk factors in overweight and obese postmenopausal women. *Diabetes Metab* 2006;32:251–255.
 19. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing. Comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462–1470.
 20. Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. *BMJ* 1990;300:230–235.
 21. Robergs RA, Dwyer D, Astorino T. Recommendations for improved data processing from expired gas analysis indirect calorimetry. *Sports Med* 2010;40:95–111.
 22. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*, 9th ed, Baltimore, MD: Lippincott Williams and Wilkins; 2014:91–92.
 23. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Executive summary. *Cardiol Rev* 2005;13:322–327.
 24. International Diabetes Federation. *The IDF Consensus Worldwide Definition of Metabolic Syndrome*. International Diabetes Federation Communications, Brussels: Belgium, 2006.
 25. Lakka TA, Laaksonen DE. Physical activity in prevention and treatment of the metabolic syndrome. *Appl Physiol Nutr Metab* 2007;32:76–88.
 26. Ortega FB, Lee DC, Katzmarzyk PT, et al. The intriguing metabolically healthy but obese phenotype: Cardiovascular prognosis and role of fitness. *Eur Heart J* 2013;34:389–397.
 27. Aspenes ST, Nilsen TI, Skaug EA, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc* 2011;43:1465–1473.
 28. Blair SN. Physical inactivity: The biggest public health problem of the 21st century. *Br J Sports Med* 2009;43:1–2.
 29. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
 30. Dalleck LC, Van Guilder GP, Richardson TB, et al. A community-based exercise intervention transitions metabolically abnormal obese adults to a metabolically healthy obese phenotype. *Diabetes Metab Syndr Obes* 2014;7:369–380.
 31. Barlow CE, Defina LF, Radford NB, et al. Cardiorespiratory fitness and long-term survival in “low-risk” adults. *J Am Heart Assoc* 2012;1:e001354.
 32. Ruderman N, Chisholm D, Pi-Sunyer X, et al. The metabolically obese, normal-weight individual revisited. *Diabetes* 1998;47:699–713.
 33. LaMonte MJ, Blair SN, Church TS. Physical activity and diabetes prevention. *J Appl Physiol* 2005;99:1205–1213.

Address correspondence to:
 Chantal A. Vella, PhD
 Department of Movement Sciences
 University of Idaho
 875 Perimeter Drive MS 2401
 Moscow, ID 83844-2401
 E-mail: cvella@uidaho.edu