Fall 2021

Clinical Determinants of VO_2 max Response to Endurance Training: HERITAGE Family Study

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Bachelor of Science
University of South Carolina, 2019

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Exercise Science

Arnold School of Public Health

University of South Carolina

2021

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ABSTRACT

Background: Maximal oxygen uptake trainability (ΔVO_2max) is largely determined by non-modifiable traits. However, less is known of the contribution of modifiable phenotypes to VO_2max response to endurance training. The purpose of this study was to examine the relationship between baseline cardiopulmonary, metabolic, and body composition traits and ΔVO_2max.

Methods: Subjects were 717 healthy, physically inactive adults (44% female, 34% Black) who completed a 20-week, highly standardized, endurance training program as part of the HERITAGE Family Study. Resting and exercise phenotypes were collected at baseline and post-training. A total of 33 variables related to cardiopulmonary, metabolic, and body composition phenotypes were entered into a forward selection model with ΔVO_2max_{abs} (mL/min) as the dependent variable. Alternative ΔVO_2max outcome regression models were performed across the study sample, including models with change in relative (mL/kg/min) and percent change in absolute and relative VO_2max. Models were then stratified by race and sex. The frequency of significant phenotypes was summed across all models. A baseline signature of ΔVO_2max_{abs} was explored using a LASSO penalized regression model with a total of 102 variables.

Results: The final model revealed 10 baseline traits significantly ($p<0.05$) associated with ΔVO_2max_{abs}. Submaximal cardiopulmonary phenotypes showed positive (e.g., cardiac output at 50 W) and negative (e.g., stroke volume index, arteriovenous oxygen difference at 50 W) associations with ΔVO_2max_{abs}. Body composition traits were also

positively (e.g., fat free mass) and negatively (e.g., abdominal visceral fat) associated with $\Delta VO_2max_{abs.}$ Resting lactate concentration was negatively associated with ΔVO_2max_{abs}. Body composition and metabolic phenotypes were consistently significant in Black and male subjects. Submaximal cardiopulmonary phenotypes were mostly significant in White and female subjects. The baseline signature of ΔVO_2max_{abs} was comprised of submaximal cardiac output and fat free mass.

Conclusion: Intrinsic values of body composition, resting lactate, and submaximal cardiopulmonary phenotypes may represent targets to maximize the cardiorespiratory fitness benefits of regular endurance exercise. Further research is needed to examine the influence of these traits on ΔVO_2max across varying exercise types and doses.

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CHAPTER 1

INTRODUCTION

Maximal oxygen uptake (VO_2max), the gold standard measurement of cardiorespiratory fitness, has been established as an important clinical diagnostic and prognostic marker of health (1). Epidemiological studies have identified strong inverse relationships between VO_2max and adverse health outcomes such as cardiovascular disease, type 2 diabetes, metabolic syndrome, and all-cause mortality (1,2). For example, individuals with high VO_2max have lower death rates for all-cause mortality and cardiovascular disease when compared those with low VO_2max (2). Furthermore, longitudinal studies have demonstrated that improving VO_2max over time is associated with significant reductions in mortality rates and morbidity risk (3–5). Given the wealth of health benefits associated with the VO_2max phenotype, improving or maintaining high VO_2max is a public health priority (1,6).

Public health efforts have been made to encourage the population to engage in regular exercise with one goal being to experience the health benefits associated with improved VO_2max (7). Among the recommended exercise modalities, endurance exercise is the principal method of improving VO_2max (8,9), with average improvements of 15-25% (10). However, standardized training studies have demonstrated that wide inter-individual variability exists in VO_2max response (ΔVO_2max) to endurance training (11–13). This variability is characterized by some individuals responding strongly to the exercise training while others respond minimally (14,15). This variability may indicate

that not all individuals may gain the health benefits associated with improved VO_2max. Thus, if a public health goal is to prescribe exercise as medicine to improve VO_2max, understanding the role of factors that influence the response of VO_2max to endurance training are vital to improve our understanding of the underlying mechanisms and the precision of exercise prescription to maximize responsiveness.

It has been widely accepted that VO_2max is dependent on cardiopulmonary, metabolic, and body composition factors for oxygen transportation and utilization. Many studies have looked at physiological phenotypes and their influence on intrinsic VO_2max (16). Other studies have focused on examining the changes in these phenotypes with endurance training (17,18). However, less is known about the contribution of intrinsic (baseline) values of these factors to ΔVO_2max in response to endurance exercise. Moreover, these physiological traits can be measured accurately and relatively inexpensively, with many already commonly measured in the clinical setting (1). Thus, the clinical utility of identifying modifiable phenotypes predictive of ΔVO_2max could assist in matching individual trait profiles with exercise prescription to maximize VO_2max responsiveness.

The purpose of this study was to identify baseline modifiable cardiopulmonary, metabolic, and body composition traits associated with ΔVO_2max in response to endurance training within a large, diverse cohort of a highly standardized training study. We sought to identify the determinants of ΔVO_2max through the following specific aims.

Aim 1: to identify baseline resting and submaximal exercise measures of modifiable cardiopulmonary, metabolic, and body composition traits associated with ΔVO_2max in response to a 20-week endurance training in healthy, previously physically

inactive adults from the HERITAGE Family Study. It is hypothesized that submaximal exercise (at 50W) cardiopulmonary phenotypes will be significant predictors of ΔVO_2max.

Aim 2: to identify a baseline signature of ΔVO_2max through feature selection of *all* modifiable phenotypes related to lipids, lipoproteins, plasma insulin and glucose, cardiopulmonary, metabolism, and body composition. We hypothesize that mostly cardiopulmonary and metabolic traits will be retained in the signature, with only a few non-cardiometabolic traits predictive of ΔVO_2max.

CHAPTER 2

LITERATURE REVIEW

Cardiorespiratory fitness (CRF) has been well established as a strong, independent predictor of morbidity and mortality(1,19). For example, studies have found consistent, inverse relationships between CRF and morbidities such as cardiovascular disease, type 2 diabetes, and obesity, as well as all-cause mortality (2). Among the factors contributing to the detrimental consequences associated with low CRF is physical inactivity (20,21). Studies investigating the relationship between physical activity and CRF have elucidated that individuals with low CRF have 67% higher all-cause mortality death rates compared to those with high CRF (3). Furthermore, physically inactive individuals with low CRF who improve to high CRF experience an approximate 40% reduction in all-cause mortality risk, a trend that is consistent across adult age groups and independent of changes in BMI(4,5). Individuals who regress from high CRF to low still show a 40% reduction in all-cause mortality risk compared to those with consistently low CRF, indicating a potential protective effect of obtaining high CRF (3). Thus, it has become a public health priority to promote CRF improvements within physically inactive adults.

Maximal oxygen uptake (VO_2max) has been widely accepted as the gold standard measurement of CRF (22). VO_2max serves as an indicator of the maximal capacity of the body to transport oxygen from the environment through pulmonary ventilation, distribute oxygen through cardiovascular circulation, and utilize oxygen in the mitochondria of

working skeletal muscles during exercise. According to the Fick principle, the two most important determinants of VO_2max are maximal cardiac output (Q; the product of heart rate (HR) and stroke volume (SV)) and arterial-venous oxygen difference (a-vO_2 difference): VO_2max = Qmax (or HRmax · SVmax) · a-VO_2 difference max. In addition to these physiological determinants, correlations between body composition factors and VO_2max have been identified. For example, fat free mass (FFM), a surrogate for skeletal muscle, is positively associated with VO_2max while body fat is negatively associated (16). Not only are these factors important in determining VO_2max but are also important in diagnosis and prognosis of cardiovascular disease, cardiopulmonary disease, heart failure, metabolic syndrome, and type 2 diabetes mellitus (1,23). This underscores the potential clinical utility of identifying modifiable cardiopulmonary, metabolic, and body composition determinants of VO_2max and, specifically, the determinants of VO_2max response to regular exercise. Determination of modifiable phenotypes could assist matching exercise prescription with individual trait profiles to maximize VO_2max responsiveness.

Objective measurements of VO_2max are assessed with the use of open circuit spirometry during a graded maximal exercise test. During exercise, the uptake of VO_2 increases linearly as work rate increases. The primary criterion for VO_2max states that the linear relationship continues until there is an observed plateau in VO_2 despite further increase in work rate (22). However, the primary criterion is not always recorded and/or not all individuals experience a plateau in VO_2. Thus, secondary criteria have been established for VO_2max that depend on measurements of other variables such as: a respiratory exchange ratio (RER) greater than 1.10, a blood lactate concentration greater

than 8.0 mmol/L, or a heart rate within 10 beats of age-predicted HRmax (HRmax=208 - 0.7 · age) (22). VO_2max values are expressed in either absolute (mL/min) or relative (mL/kg/min) terms. Although maximal exercise tests with open circuit spirometry may provide the most accurate measurement of VO_2max, these tests are expensive and physically demanding on the participant. Therefore, maximal exercise testing may not be suitable for all populations or across clinical settings (22). Furthermore, using a maximal exercise test would be less practical if the objective is to discern predictors of VO_2max and its response to regular exercise. A submaximal exercise test with direct gas exchange measurements may serve as an effective alternative. Submaximal exercise testing reduces the physical burden on participants requiring a lower exercise intensity at two or more workloads. Heart rate response measures are recorded once steady state has been achieved at each workload stage (approximately 3 minutes). The linear relationship between heart rate and each workload is used to extrapolate the VO_2max value. Studies have demonstrated that submaximal exercise prediction equations of VO_2max are moderately to highly accurate when used with direct gas exchange measurements (24). Therefore, clinical and fitness settings would benefit from the objective assessment of VO_2max with open circuit spirometry through submaximal exercise testing. Additionally, submaximal exercise testing may be better suited for identifying modifiable phenotypes that are predictive of VO_2max and its response to regular exercise.

An abundance of evidence has demonstrated the health benefits associated with improving VO_2max by living a physically active lifestyle and, specifically, participating in regular exercise (6,25,26). As a result, national public health recommendations emphasize the importance of regularly engaging in both endurance and strength-related

physical activity and/or exercise to improve VO_2max (7,26). Resistance training has been shown to provide moderate improvements to VO_2max (12); however, endurance training serves as the primary exercise method to improve VO_2max (8,9). The average improvement in VO_2max following an endurance exercise training program can range from 15-25% (10). Standardized endurance training studies have demonstrated, however, that a wide variation of VO_2max responses to training exists between individuals (11,12), with values ranging from large improvements to no improvements/slight decreases (14,27). Considering the importance of CRF as a strong predictor of morbidity and mortality, the heterogeneity of ΔVO_2max in response to endurance training could indicate that low- and non-responsive individuals may not gain all of the health benefits associated with increased VO_2max. Thus, it is important to establish the factors that contribute to this heterogeneity.

Previous investigations have provided information on non-modifiable determinants of ΔVO_2max variability. The HERITAGE Family Study examined the influence of genetics on cardiometabolic responses to standardized endurance training within a cohort of healthy, previously physically inactive adults (11). After a 20-week training period, approximately 47% of the variability of VO_2max response to endurance exercise was accounted for by genetic and shared environmental factors after adjusting for age and sex (28). However, the contribution of other, non-modifiable determinants of VO_2max trainability such as race, age, and sex were approximately 9%, collectively (29). Furthermore, other studies found that modifiable phenotypes such as initial VO_2max and bodyweight contributed approximately 2% and 3%, respectively, to the variance of

ΔVO_2max in HERITAGE (30). Despite the existing evidence, a portion of the interindividual variance of ΔVO_2max still remains undetermined.

As stated previously, VO_2max is a complex phenotype that has physiological determinants and correlates of modifiable nature. However, less is known of the contribution of intrinsic (baseline) values of modifiable phenotypes to the variation of ΔVO_2max in response to standardized endurance training. Of particular interest are physiologically and clinically relevant phenotypes, such as cardiopulmonary, metabolic, and body composition traits, as these are known to be associated with and/or involved in oxygen consumption during exercise. Moreover, these traits can be measured accurately and relatively inexpensively, with many already commonly measured in the clinical setting. Therefore, it is evident that there is a need to identify modifiable baseline determinants of ΔVO_2max related to cardiopulmonary, metabolic, and body composition phenotypes within in a diverse population of adults to maximize VO_2max responsiveness to endurance training.

CHAPTER 3

METHODOLOGY

HERITAGE Family Study. The HERITAGE Family Study (hereafter referred to as HERITAGE) is one of the largest, most well-controlled, standardized exercise training studies to date. The study design, subject inclusion and exclusion criteria, and endurance training program have been described previously (31). Briefly, HERITAGE recruited two-generational families of European or African descent (hereafter Whites and Blacks) to one of four clinical centers (Bloomington, IN; Minneapolis, MN; Austin, TX; Laval, Quebec) to complete a 20-week endurance training program. Subjects were between the ages of 17-65, physically inactive at baseline, but otherwise healthy with a body mass index (BMI) below 40 kg/m^2, normotensive or mildly hypertensive (<160/100 mmHg), and free of medications for diabetes, hypertension, or dyslipidemia. Written informed consent was collected from all subjects. A total of 742 subjects completed the HERITAGE training program.

Training Program. Details of the standardized exercise training protocol can be found elsewhere (31). In brief, subjects trained on a stationary cycle ergometer (Universal Aerobicycle) three sessions per week for 20 weeks. Subjects began training at 55% VO_2max for 30 min/session. The intensity and duration were progressively incremented every two weeks until the last six weeks where subjects trained at 75% VO_2max for 55 min/session.

Exercise Testing. Subjects completed three exercise testing protocols (graded maximal, steady-state submaximal, and submaximal-maximal) at baseline and post-training on a cycle ergometer at approximately the same time of day with at least 48 hours difference between tests. For the graded maximal test, initial intensity was set to 50 Watts (W) and increased by 25 W every two minutes until VO_2max criteria was met. In the steady-state submaximal test, subjects pedaled for 10-12 minutes at a 50 W and 60% VO_2max power output. The submaximal-maximal test, performed on a third day, started with the submaximal test protocol followed by an increase to maximal level of exertion until volitional exhaustion. VO_2max criteria was defined as: VO_2 uptake plateau, respiratory end ratio (RER)>1.1, heart rate (HR) within 10 BPM of age predicted HRmax. All subjects met at least one of these criteria on at least one of the maximal tests. The final VO_2max value per timepoint was determined as an average of the two maximal tests when the difference between the values was less than 5%. The highest VO_2max value was used when the difference between values was greater than 5%. ΔVO_2max was calculated as the difference between the post-training and baseline VO_2max value.

Body composition measurements. Body composition measurements were collected once at baseline and post-training, as previously described (32). Briefly, anthropometric measurements of body weight, skinfold thickness, and height were recorded. Body density, fat-free mass (FFM), fat mass, and percent body fat (%fat) were assessed through hydrostatic weighing. %fat was estimated using specific equations for white males (33), white females (34) black males (35), and black females (36). Computed axial tomography (CT) scans were performed to calculate abdominal visceral (AVF), subcutaneous, and total fat areas as previously described (37).

Cardiopulmonary measurements. The blood pressure (BP) and HR measurement protocols succinctly presented here have been previously described (38). Resting BP measures were recorded with an automatic BP cuff (Colin STBP-780) on two separate days at baseline and at 24 hours and 72 hours post-training while subjects were in a semi-recumbent position. An electrocardiogram (ECG) linked to the BP cuff was used to monitor HR at rest and during all exercise testing. An average of two HR values was recorded for the submaximal intensities (i.e. 50 W and 60% VO_2max) at baseline and post-training exercise testing. Cardiac output (Q) was determined using the Collier CO_2 rebreathing technique as previously described (39). Stroke volume (SV) was determined by dividing Q by HR (SV=Q/HR). Other factors such as, mean arterial pressure (MAP), cardiac index (CI), SV index (SVI), and total peripheral resistance (TPR) were derived from Q and BP measurements. Gas exchange values were recorded as rolling averages of three, 20-second intervals (VO_2, VCO_2, ventilation, RER) with the use of a metabolic cart (SensorMedic 2900) during exercise tests. Hemoglobin and hematocrit concentrations were quantified during whole blood sampling procedures.

Metabolic substrates measurements. Blood samples were collected from the antecubital vein at rest, during each workload of exercise testing, and immediately after completing the exercise test. Concentrations of free fatty acids, glucose, and lactate were quantified from blood sampling. For the current study, only baseline values at rest and submaximal (50 W) will be used for analysis.

Lipids and lipoprotein measurements. A blood draw was performed in the morning after a 12-hour, overnight fast, on two separate days at baseline and 24 hours and 72 hours after the last training bout. Fasting blood samples were collected through a

venous catheter placed in the antecubital vein and were stored in vacutainer tubes containing EDTA (40). Whole blood samples were placed in an ultracentrifuge to isolate very low-density lipoprotein (VLDL). Infranatant precipitation of low-density lipoprotein (LDL) was performed using the heparin-manganese chloride method (41). High-density lipoprotein (HDL) was collected thereafter. HDL subfractions were selectively precipitated from the infranatant using dextran sulfate. Total cholesterol and triglycerides (TG) levels were determined in plasma and lipoprotein fractions by enzymatic methods using the Technicon RA-1000 analyzer. Concentrations of apolipoprotein (apo) A-1 and apoB in plasma and infranatant fractions were measured by rocket-immunoelectrophoretic method. Nuclear magnetic resonance (NMR) spectroscopy was conducted at LabCorp, Inc (Morrisville, N.C.) for complex lipoprotein subfraction analysis (e.g., concentration of large, medium, small HDL and LDL particles) of fasting plasma samples using the LipoProfile-4 algorithm (42).

Plasma insulin and glucose measurements. Following a 12-hour fasting period, subjects completed an intravenous glucose tolerance test (IVGTT) at baseline and 24- and 72-hours post-training as described previously (43). In brief, blood samples were collected from the antecubital vein at 16 different timepoints over the span of 3 hours. Concentrations of plasma glucose were determined enzymatically; plasma insulin and connecting peptide (C-peptide) concentrations were determined by polyethylene glycol separation method (31). Insulin sensitivity (Si), glucose effectiveness (Sg), and related traits were quantified with the MINMOD Millennium software (44).

Current study sample. The current study sample consisted of subjects from HERITAGE who: completed the 20-week endurance training program; had valid ΔVO_2max

measurements; and had at least 90% complete data for select phenotypes. A total of 33 baseline cardiopulmonary, body composition, and metabolic phenotypes measured at rest and during submaximal exercise at 50 W were included for the primary analysis (Table 3.1). These phenotypes were selected as they are known to be associated with and/or involved in oxygen consumption during exercise. An additional 66 modifiable phenotypes related to plasma lipids, lipoproteins, insulin, and glucose were included for a subsequent analysis of the baseline signature for ΔVO_2max as these factors may be indirectly involved in the response of oxygen consumption to exercise training (Table 3.2).

Statistical Analysis. Data imputation was performed using k-nearest neighbors' method for subjects with at least 90% complete data. To identify modifiable, clinically relevant factors associated with ΔVO_2max absolute or ΔVO_2max_{abs} (mL/min), 33 phenotypes were entered into forward selection regression models as independent variables. The contribution of non-modifiable factors age, sex, and race were accounted for by forcing these variables into the model. Variables associated with ΔVO_2max_{abs} at a significance level of $p<0.05$ were retained in the model. The stability of identified variables was examined across race- and sex-specific models, as well as alternative models that included different outcome variables: ΔVO_2max relative or ΔVO_2max_{rel} (mL/kg/min), $\%\Delta VO_2max_{abs}$, and $\%\Delta VO_2max_{rel}$. A least absolute shrinkage and selection operator (LASSO) penalized multiple regression model was used to identify a baseline signature of ΔVO_2max_{abs} that included 66 variables related to other modifiable, physiological phenotypes in addition to the 33 variables from the primary analysis. The tuning

parameter was identified with a 10-fold random cross-validation. All models were analyzed using SAS software (Version 9.4, SAS Institute Inc., Cary, NC, USA).

Table 3.1 Baseline resting and submaximal exercise phenotypes included in final regression model.

Resting (n=14 phenotypes)				
Mean Arterial Pressure	Rate Pressure Product	Hematocrit	Lactate	%Fat
Diastolic Blood Pressure	Heart Rate	Free Fatty Acids	Abdominal Visceral Fat	Fat Free Mass
Systolic Blood Pressure	Hemoglobin	Glucose	Fat Mass	
Submaximal Exercise at 50 W (n=19 phenotypes)				
Mean Arterial Pressure	Rate Pressure Product	Cardiac Index	VO_2	Free Fatty Acids
Diastolic Blood Pressure	Heart Rate	Stroke Volume Index	VCO_2	Glucose
Systolic Blood Pressure	Stroke Volume	a-vO_2 difference	Ventilation	Lactate
Total Peripheral Resistance	Cardiac Output	Respiratory End Ratio	Tidal Volume	

Table 3.2 Additional modifiable phenotypes included as variables in the LASSO regression model.

HDL-C	HDL Size
Apolipoprotein A-I	Total BCAA
Triglycerides (TG)	Valine
Hepatic Lipase Activity (HL)	Leucine
Lipoprotein Lipase Activity (LPL)	Isoleucine
HL/LPL Log Ratio	Alanine
HDL2-C	Glucose
HDL3-C	Citrate
HDL-TG	Total Ketone Bodies
LDL-C	Beta-hydroxy-butyrate
LDL-TG	Aceto-acetate
Total Plasma Cholesterol	Acetone
VLDL-C	Protein
Apolipoprotein B (ApoB)	GlycA Concentration
LDL apoB	C-reactive Protein
VLDL apoB	Total Fat Area
VLDL-TG	Subcutaneous Fat Area
Triglyceride-Rich Lipoprotein (TRLP) Particle Concentration	Body Mass Index
Very Large TRLP Concentration	Body Surface Area
Large TRLP Concentration	Weight
Medium TRLP Concentration	Waist Circumference
Small TRLP Concentration	Waist/Hip Ratio
Very Small TRLP Concentration	Abdominal Skinfold Average
Calibrated total LDL Partcle (cLDLP) Concentration	8 Skinfold Sum
Large cLDLP Concentration	Trunk and Extremity Skinfold Ratio
Medium cLDLP Concentration	Acute Insulin Response to Glucose
Small cLDLP Concentration	Disposition Index
Calibrated total HDL Particle (cHDLP) Concentrations	Fasting Glucose
Large cHDLP Concentration	Glucose Effectiveness
Medium cHDLP Concentration	Insulin Sensitivity Index
Small cHDLP Concentration	Fasting Insulin
Triglyceride-Rich Lipoprotein (TRL) Size	Leptin
LDL Size	Leptin at 50 W

The least absolute shrinkage and selection operator (LASSO) regression model contained a total of 102 variables: 66 variables were related to lipids, lipoproteins, metabolism, and body composition; 33 variables were from the forward selection model; age, sex, and race were also entered as variables.

CHAPTER 4

RESULTS

Descriptive statistics. Study subject demographics and phenotype measurements are presented in Table 4.1. A total of 717 subjects comprised the current study sample, consisting of 44% males and 34% Black. The average age was 35 years and BMI 26.47 kg/m^2. VO_2max increased an average of 385 mL/min, 5 mL/kg/min, and about 17-18% with training.

Baseline cardiometabolic determinants of ΔVO_2max.

ΔVO_2max_{abs}. The primary focus of the study was to discern intrinsic determinants of ΔVO_2max_{abs} from 33 baseline, modifiable phenotypes. Our analysis revealed five cardiopulmonary, four body composition, and one metabolic phenotype significantly associated with ΔVO_2max_{abs}, after accounting for the effects of race, sex, and age (Table 4.2). Four of the cardiopulmonary variables were submaximal phenotypes, while all other significant variables were resting measures. Three of the identified cardiopulmonary measures (i.e., hemoglobin, submaximal Q, and ventilation), along with FFM and %fat, were positively associated with ΔVO_2max_{abs}. Fat mass, AVF, and resting lactate were negatively associated with $\Delta VO_2max_{abs.}$

ΔVO_2max_{rel}. We then examined the relationship between the 33 independent variables and ΔVO_2max_{rel}. One metabolic, one body composition, and three cardiopulmonary variables were significantly associated with ΔVO_2max_{rel} (Table 4.3). Two cardiopulmonary traits (submaximal Q, hemoglobin) were positively associated,

while submaximal a-vO_2 difference, resting lactate, and AVF were negatively associated with ΔVO_2max.

%ΔVO_2max_{abs}. Four cardiopulmonary and two metabolic phenotypes were identified as significant determinants of $\%\Delta VO_2max_{abs}$ (Table 4.4). Submaximal measures of HR, RER, and lactate were positively associated with $\%\Delta VO_2max_{abs}$. Consistent with previous models, some submaximal cardiopulmonary (a-vO_2 difference, SVI) and resting lactate were negatively associated with $\%\Delta VO_2max_{abs}$.

%ΔVO_2max_{rel}. Five cardiopulmonary and two metabolic variables were significantly associated with $\%\Delta VO_2max_{rel}$ (Table 4.5). Positive associations were identified for submaximal cardiopulmonary (DBP, HR, RER) and submaximal measures of lactate. Negatively associated variables were submaximal SVI, a-vO_2 difference, and resting lactate.

Determinants of ΔVO_2max by race.

Black subjects. Negative associations were consistently identified for AVF in all four outcome variable models in Black subjects (Table 4.6). Resting and submaximal measures of lactate showed negative and positive associations, respectively, with all VO_2max response except ΔVO_2max_{rel}. Submaximal HR measures were positively associated with VO_2max response across all outcome models except ΔVO_2max_{abs}. No cardiopulmonary measures were identified as significantly associated with ΔVO_2max_{abs} in Black subjects.

White subjects. Submaximal cardiopulmonary phenotypes were consistently identified as significantly associated with ΔVO_2max across models in White subjects (Table 4.7). Positive associations were found for submaximal Q and HR across most

models. Other frequently observed submaximal variables (e.g., a-vO_2 difference, SVI). were negatively associated with most VO_2max response outcomes. In the models of %ΔVO_2max_{abs} and %ΔVO_2max_{rel}, submaximal cardiopulmonary variables were the only significant phenotype category identified. The only body composition phenotype identified in White subjects as having a significantly negative association with ΔVO_2max_{abs} and ΔVO_2max_{rel} was AVF.

Determinants of ΔVO_2max by sex.

***Male subjects*.** We further examined the determinants of VO_2max response across all outcome models by stratifying by sex. In males, submaximal cardiopulmonary phenotypes were consistently identified as determinants (Table 4.8). Submaximal a-vO_2 difference was negatively associated with all VO_2max response variables except ΔVO_2max_{abs}. Percent fat was consistently positively associated with all VO_2max response variables except ΔVO_2max_{rel}. ΔVO_2max was negatively associated with resting glucose concentrations in all models but ΔVO_2max_{abs} for male subjects.

***Female subjects*.** Cardiopulmonary phenotypes measured during submaximal exercise were consistently associated with ΔVO_2max in all outcome models in female subjects (Table 4.9). Most of these submaximal measures were positively associated (e.g., HR and RER), while others were negatively associated (e.g., a-vO_2 difference and SVI). Negative associations were found for AVF with ΔVO_2max in all models except ΔVO_2max_{rel}. Resting lactate was the only phenotype identified as negatively associated with VO_2max response in all female-specific models.

Consistency of baseline determinants of ΔVO_2max across models. Across 20 stepwise selection models, submaximal measures of HR and a-vO_2 difference were both identified

as significantly associated with VO_2max response in 13 models. The phenotypes AVF and resting lactate were both significantly associated with VO_2max response across 12 models. All other variables appeared in less than 50% of the models. Across whole group models, submaximal a-vO_2 difference and resting lactate were identified in all outcome groups. Submaximal HR and SVI were identified in three of four groups. Race-specific models showed that White subjects had larger number of cardiopulmonary factors that overlapped with main group analysis of ΔVO_2max_{abs} and ΔVO_2max_{rel} models, when compared to Black subjects. Black subjects had consistent overlapping factors of AVF and lactate at rest and submaximal exercise with models. Black subjects showed greater number of overlapping of factors in the $\%\Delta VO_2max_{rel}$ model, compared to White subjects. Subgroup analysis by sex demonstrated that female subjects also had a larger number of overlapping factors with the main group analysis when compared to male subjects across all models except $\%\Delta VO_2max_{rel}$. When comparing overlapping factors between white and black subjects, submaximal HR overlapped across the relative and percent change models. Two models (ΔVO_2max Abs, Rel) showed AVF overlapping for both race groups. Submaximal a-vO_2 difference was the only phenotype consistently identified in two models (Rel and %Abs.) between male and female subjects. Some patterns emerged over the different outcome models. Submaximal Q was a commonly found as significant in ΔVO_2max_{abs} models, however, when using non-absolute outcomes, cardiac output seemed to be replaced by submaximal HR. This pattern was also identified in the female-specific absolute and non-absolute models. Body composition phenotype AVF held a significant association with ΔVO_2max_{abs} and ΔVO_2max_{rel}. This pattern was also observed in White subjects. Only female subjects

showed resting lactate as significant in all models. This was similar to the pattern observed in whole group analysis.

ΔVO_2max baseline signature. In an exploratory approach to identify a baseline signature of ΔVO_2max, 102 variables were analyzed using LASSO penalized regression. Two variables had non-zero beta coefficient values in the model: Q 50 and FFM. Furthermore, we explored the feature selection function of LASSO by applying it to the 33 phenotypes from the primary analysis. The identified signature consisted of one body composition (FFM) and two cardiopulmonary (Q 50, hemoglobin) phenotypes. All three variables showed a positive contribution to ΔVO_2max.

Table 4.1 Baseline characteristics and VO_2max responses to training.

Characteristic	Total (n=717) Mean (SD)	Males (n=317) Mean (SD)	Females (n=400) Mean (SD)
Race (Black / White)	317 / 400	87 / 230	159 / 241
Age (years)	35.0 (13.6)	36.1 (14.4)	34.1(12.9)
BMI (kg/m^2)	26.5 (5.3)	26.8 (4.9)	26.2 (5.6)
Fat Percent (%)	28.0 (10.2)	23.1 (8.6)	32.0 (9.6)
DBP (mm Hg)	68.2 (8.7)	69.4 (8.5)	67.2 (8.8)
SBP (mm Hg)	118.4 (11.7)	121.0 (10.6)	116.3 (12.1)
VO_2max_{abs} (mL/min)	2331.6 (725.1)	2947.4 (586.7)	1843.55 (361.6)
ΔVO_2max_{abs} (mL/min)	384.9 (202.0)	437.1 (227.2)	343.5 (168.7)
VO_2max_{rel} (mL/kg/min)	31.2 (8.8)	36.0 (8.6)	27.4 (6.9)
ΔVO_2max_{rel} (mL/kg/min)	5.3 (2.9)	5.5 (3.1)	5.1 (2.7)
$\%\Delta VO_2max_{abs}$	17.6 (9.5)	15.4 (8.2)	19.8 (10.0)
$\%\Delta VO_2max_{rel}$	18.1 (10.2)	15.9 (9.0)	19.8 (10.9)

Table 4.2 Clinical determinants of ΔVO_2max_{abs} resulting from final regression model.

Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex, Race			0.0669	
Cardiac Output 50 W	12.70142	0.0307	0.0976	<.0001
Stroke Volume Index 50 W	-6.18372	0.0242	0.1217	<.0001
Abdominal Visceral Fat	-0.76028	0.0113	0.133	0.0024
% Fat	9.68189	0.0085	0.1415	0.0084
Fat Free Mass	6.59708	0.0074	0.1489	0.0135
a-vO_2 difference 50 W	-5.3787	0.0114	0.1603	0.002
Hemoglobin	18.08023	0.0058	0.1661	0.0271
Ventilation 50 W	4.33947	0.0058	0.1719	0.0261
Lactate	-48.18493	0.0051	0.177	0.0374
Fat Mass	-5.89464	0.0051	0.1821	0.0362

A total of 33 variables were entered into the model along with age, sex, and race which were forced into the final model.

Table 4.3 Clinical determinants associated with ΔVO_2max_{rel} in alternative outcome regression model.

Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex, Race			0.039	
Abdominal Visceral Fat	-0.00977	0.0278	0.0668	<.0001
Heart Rate 50 W	0.03971	0.0294	0.0962	<.0001
a-vO_2 difference 50 W	-0.04517	0.0147	0.111	0.0006
Lactate	-0.97117	0.0097	0.1207	0.0052
Hemoglobin	0.24789	0.0077	0.1284	0.0126

The forward selection model consisted of 33 cardiometabolic and body composition variables. Age, sex, and race were forced into the model.

Table 4.4 Clinical determinants associated with $\%\Delta VO_2max_{abs}$ in alternative outcome regression model.

Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex, Race			0.0601	
Heart Rate at 50 W	0.00053816	0.0592	0.1193	<.0001
Respiratory End Ratio 50 W	0.28996	0.0233	0.1426	<.0001
a-vO_2 difference 50 W	-0.00211	0.0113	0.1538	0.0022
Lactate	-0.04342	0.0096	0.1634	0.0045
Stroke Volume Index 50 W	-0.0024	0.0111	0.1746	0.0021
Lactate 50 W	0.01553	0.0063	0.1809	0.02

The forward selection model consisted of 33 independent variables related to cardiopulmonary, metabolic, and body composition phenotypes. Age, sex, and race were variables that were forced into the model.

Table 4.5 Clinical determinants associated with $\%\Delta VO_2max_{rel}$ in alternative outcome regression model.

Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex, Race			0.0535	
Heart Rate at 50 W	0.00026463	0.0599	0.1134	<.0001
a-vO_2 difference 50 W	-0.00267	0.0109	0.1243	0.003
Stroke Volume Index 50 W	-0.00352	0.0172	0.1415	0.0002
Lactate	-0.05453	0.0137	0.1552	0.0007
Lactate 50 W	0.0194	0.0138	0.169	0.0006
Respiratory End Ratio 50 W	0.19622	0.0052	0.1742	0.0351
Diastolic Blood Pressure 50 W	0.00080588	0.0047	0.1789	0.0448

A total of 33 cardiometabolic and body composition phenotypes were included as independent variables with age, sex, and race forced into the model.

Table 4.6 Clinical determinants associated with ΔVO_2max across four regression models for Black subjects.

ΔVO_2max_{abs}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0428	
Lactate 50 W	54.43554	0.0276	0.0704	0.0079
% Fat	6.60866	0.0264	0.0968	0.0084
Abdominal Visceral Fat	-0.99262	0.0358	0.1326	0.0019
Lactate	-73.89985	0.0149	0.1475	0.042
ΔVO_2max_{rel}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0079	
Fat Free Mass	-0.04791	0.0715	0.0794	<.0001
Abdominal Visceral Fat	-0.0128	0.0282	0.1076	0.0062
Heart Rate 50 W	0.03167	0.0343	0.1419	0.0022
$\%\Delta VO_2max_{abs}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0867	
Heart Rate 50 W	0.00152	0.0935	0.1802	<.0001
Respiratory End Ratio 50 W	1.96738	0.0379	0.2181	0.0007
Lactate	-0.07651	0.0244	0.2425	0.0059
Lactate 50 W	0.02893	0.024	0.2665	0.0056
Abdominal Visceral Fat	-0.00050659	0.0129	0.2794	0.0401
% Fat	0.00337	0.0239	0.3033	0.0047
Volume Carbon Dioxide 50 W	-0.00165	0.0145	0.3178	0.0261
Volume Oxygen 50 W	0.0014	0.0124	0.3302	0.0379
$\%\Delta VO_2max_{rel}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0827	
Heart Rate 50 W	0.00182	0.096	0.1787	<.0001
Lactate	-0.08617	0.0229	0.2016	0.0092
Lactate 50 W	0.03981	0.0416	0.2432	0.0003
Volume Oxygen 50 W	-0.00016763	0.0142	0.2574	0.0333
% Fat	0.00337	0.0193	0.2767	0.0124
Abdominal Visceral Fat	-0.00043024	0.0158	0.2925	0.0224

For each model, 33 phenotypes were included as independent variables. The effects of age and sex were accounted by forcing these variables into the models.

Table 4.7 Clinical determinants associated with ΔVO_2max across four regression models for White subjects.

ΔVO_2max_{abs}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0732	
Cardiac Output 50 W	90.23391	0.0499	0.1231	<.0001
Stroke Volume Index 50 W	-12.00178	0.028	0.1511	0.0001
Rate Pressure Product 50 W	-0.0196	0.0145	0.1656	0.0046
Abdominal Visceral Fat	-0.5955	0.0102	0.1758	0.0169
Total Peripheral Resistance 50 W	35.6452	0.0081	0.1839	0.0327
a-vO_2 difference 50 W	-3.02051	0.0075	0.1914	0.0395
Hemoglobin	20.42177	0.0087	0.2001	0.0254
ΔVO_2max_{rel}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0434	
a-vO_2 difference 50 W	-0.04085	0.0239	0.0673	0.0006
Heart Rate at 50 W	0.03452	0.0199	0.0872	0.0015
Lactate	-0.92437	0.0115	0.0988	0.0152
Abdominal Visceral Fat	-0.00667	0.0078	0.1065	0.0449
$\%\Delta VO_2max_{abs}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0392	
Heart Rate 50 W	0.00020216	0.0394	0.0786	<.0001
a-vO_2 difference 50 W	-0.0017	0.0173	0.0958	0.003
Respiratory End Ratio 50 W	0.26753	0.0138	0.1096	0.0075
Stroke Volume Index 50 W	-0.00307	0.0125	0.1222	0.0104
Cardiac Output 50 W	0.00894	0.0104	0.1325	0.019
$\%\Delta VO_2max_{rel}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Sex			0.0312	
Heart Rate 50 W	0.00028621	0.0388	0.07	<.0001
Cardiac Output 50 W	0.02583	0.0111	0.0811	0.018
Stroke Volume Index 50 W	-0.00381	0.0114	0.0925	0.016
Volume Oxygen 50 W	-0.00017614	0.0225	0.115	0.0006

A total of 33 variables related to cardiopulmonary, metabolic, and body composition phenotypes were included in each model. Age and sex were forced into the models as independent variables.

Table 4.8 Clinical determinants associated with ΔVO_2max across four regression models for male subjects.

ΔVO_2max_{abs}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0315	
Cardiac Output 50 W	26.68965	0.0305	0.062	0.0016
% Fat	8.55551	0.0286	0.0906	0.0019
Abdominal Visceral Fat	-0.8389	0.0175	0.108	0.0141
ΔVO_2max_{rel}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0453	
a-vO_2 difference 50 W	-0.07219	0.0341	0.0794	0.0007
Glucose	-0.52441	0.0289	0.1082	0.0016
Diastolic Blood Pressure 50 W	0.0403	0.014	0.1222	0.0269
Stroke Volume 50 W	-0.0261	0.013	0.1352	0.0313
$\%\Delta VO_2max_{abs}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.002	
Respiratory End Ratio 50 W	0.32313	0.0297	0.0317	0.0021
% Fat	0.00251	0.0213	0.0531	0.0084
a-vO_2 difference 50 W	-0.00134	0.0331	0.0862	0.0009
Glucose	-0.01213	0.0166	0.1028	0.0173
$\%\Delta VO_2max_{rel}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0033	
Heart Rate 50 W	0.00034956	0.0207	0.024	0.0104
Glucose	-0.01638	0.0184	0.0423	0.015
a-vO_2 difference 50 W	-0.00222	0.0141	0.0564	0.032
% Fat	0.00162	0.0263	0.0827	0.0031
Stroke Volume Index 50 W	-0.00213	0.0119	0.0946	0.0449

Each model included 33 cardiometabolic and body composition phenotypes as independent variables. Age and race were forced into the models.

Table 4.9 Clinical determinants associated with ΔVO_2max across four regression models for female subjects.

ΔVO_2max_{abs}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0035	
Cardiac Output 50 W	30.90371	0.0303	0.0338	0.0005
Stroke Volume Index 50 W	-9.1631	0.0409	0.0747	<.0001
Abdominal Visceral Fat	-1.04389	0.0334	0.108	0.0001
Hematocrit	7.59673	0.0136	0.1216	0.014
Lactate	-79.01758	0.0087	0.1304	0.0479
a-vO_2 difference 50 W	-2.93192	0.0108	0.1412	0.0272
Fat Free Mass	5.29614	0.0133	0.1545	0.0136
Respiratory End Ratio 50 W	403.55452	0.01	0.1645	0.0318
ΔVO_2max_{rel}				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.028	
Heart Rate 50 W	0.04653	0.0477	0.0757	<.0001
Abdominal Visceral Fat	-0.01154	0.0312	0.1068	0.0002
Lactate	-1.19669	0.0142	0.121	0.0122
a-vO_2 difference 50 W	-0.04032	0.0105	0.1315	0.0295
Hematocrit	0.11369	0.0137	0.1453	0.0124
$\%\Delta VO_2max_{abs}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0318	
Heart Rate 50 W	0.00045162	0.0856	0.1174	<.0001
Respiratory End Ratio 50 W	0.37688	0.0253	0.1427	0.0007
Lactate	-0.05429	0.021	0.1637	0.0018
Abdominal Visceral Fat	-0.00037935	0.0083	0.172	0.0479
Stroke Volume Index 50 W	-0.00481	0.0091	0.1811	0.0376
a-vO_2 difference 50 W	-0.00262	0.0315	0.2126	<.0001
$\%\Delta VO_2max_{rel}$				
Variable	Parameter Estimates	Partial R^2	Model R^2	p-value
Age, Race			0.0374	
Heart Rate 50 W	0.00173	0.0892	0.1266	<.0001
Lactate	-0.05604	0.0151	0.1417	0.0088
Respiratory End Ratio 50 W	0.34764	0.0185	0.1603	0.0034

The independent variables for each regression model consisted of 33 variables related to cardiopulmonary, metabolic, and body composition traits. The age and race were forced into the models as independent variables.

CHAPTER 5

DISCUSSION

The main finding of this study was that 10 baseline traits related to the cardiopulmonary system, metabolism, and body composition were significantly associated with ΔVO_2max_{abs}. Traits were examined across four ΔVO_2max phenotypes in the total sample and models stratified by race and sex. The phenotypes identified most frequently across models were HR 50, a-vO_2 difference 50, AVF, and resting lactate. Moreover, LASSO analysis identified a two variable baseline signature of ΔVO_2max_{abs} comprised of Q 50 and FFM.

The volume of oxygen uptake is directly limited by the ability of the cardiovascular system to transport oxygen from the environment to the working skeletal muscles during exercise. The Fick principle defines VO_2 uptake as the product of Q and a-vO_2 difference, where Q is the product of HR and SV. Clearly, these factors are primary determinants of VO_2max. The results from our study indicate that these cardiovascular factors measured during a steady-state submaximal exercise test may also serve as determinants of ΔVO_2max. Our final model showed that Q and HR at 50W were positively associated with ΔVO_2max_{abs}. It has been well established that Q increases as HR and SV increase at the start of a bout of exercise. A plateau in HR, SV, and Q is expected during a steady-state submaximal exercise test. This plateau may serve as a reflection of the efficiency of the cardiovascular system to meet the metabolic demand of

exercise. Our findings suggest that a higher baseline submaximal Q or HR can be indicative of an individual whose heart is less adapted to exercise stressors, therefore potentially indicating that a larger VO_2max response to endurance training could be expected since the individual's baseline cardiovascular system is less efficient and has more room to improve.

A negative association between SVI and VO_2max response was identified frequently within our results. The SVI value quantifies the total volume of blood that is ejected from the left ventricle per m^2 of body surface area (BSA). Higher values of SVI at baseline would indicate a heart that is more effective at distributing oxygenated blood to meet the physiological demand according to the workload. The mechanisms regulating higher baseline SV could be attributed to increased preload (45), increased contractility by sympathetic stimulus (46), and decreased aortic pressure (47). Thus, an increased submaximal exercise SVI prior to exercise training represents an increased ability to effectively circulate blood across the body, which may result in a smaller increase of VO_2max in response to endurance training since the heart is already performing efficiently and may have less ability for further improvements.

The measure of a-vO_2 difference reflects the effectiveness of peripheral tissue (e.g., skeletal muscles) to extract oxygen from blood. The results from our study indicate that as baseline submaximal a-vO_2 difference increases, there is a direct reduction in the response of VO_2max to endurance training. An above average intrinsic a-vO_2 difference value could be explained by potential mechanisms such as increased capillary density, mitochondrial density, and myoglobin function (48). With an increased submaximal a-vO_2 difference at baseline, there may be less ability to further expand a-vO_2 difference

with training. Indeed, in HERITAGE the correlation between baseline and change in a-vO_2 difference at 50W was negative ($r = -0.43$, $p<0.0001$). Furthermore, an increased efficiency for oxygen extraction may suggest that an increased VO_2max value at baseline is possible. Therefore, higher baseline VO_2max values due to an increased a-vO_2 difference could result in smaller magnitude response of VO_2max as the efficiency of oxygen uptake and utilization may be close to the physiological limit.

It has been well established that body composition influences VO_2max. Our final model showed that all four body composition traits included in the model were significant determinants of ΔVO_2max. Among these, we identified positive associations between FFM and ΔVO_2max_{abs} in the main model, but sparingly throughout the alternative outcome models. Our findings indicate that the greater the baseline FFM, the greater the VO_2max response to training. This is logical since skeletal muscle is the main component of FFM. Thus, higher FFM is associated with higher skeletal muscle mass (49), which could indicate increased oxidative metabolism ability that would benefit exercise performance, including VO_2max. Previous studies have corroborated the positive relationship between FFM and VO_2max (50). Thus, larger baseline amounts of FFM may indicate a favorable body composition component for an increased response to endurance training.

During exercise, oxidative phosphorylation processes in the muscles are fueled by metabolism of glucose/glycogen and fatty acids. Adipose tissue is the primary source of fatty acids during exercise. The results obtained here show a negative association between baseline AVF and VO_2max response across multiple models. Excessive accumulation of AVF has been associated with increased risk of developing multiple

cardiometabolic diseases (51). Although AVF may serve as a fuel source during exercise, studies have shown that the contribution of fatty acids from AVF are less than 10% (52). A study performed by Shioya-Yamada looked at the relationship between the effects of augmented AVF on exercise tolerance in Japanese men. Their results showed that AVF was negatively associated with exercise ability. The group concluded that AVF may indirectly affect exercise tolerance by a cascade of events that result in the release of inflammatory markers such as tumor necrosis factor-alpha, which lead to decreased functionality of skeletal muscles (53). Approaching our finding from this perspective, increased AVF identified at baseline may impair the oxidative phosphorylation ability of skeletal muscle, which could reduce VO_2max and its response to endurance training.

Our results frequently demonstrated a negative association between resting lactate concentrations and ΔVO_2max. Lactate is continuously produced by cells within the body as a product of metabolic processes. During exercise, lactate concentrations increase as a product of glycolysis. The accumulation of lactate at rest can be caused by an increased production, a decreased rate of clearance, or a combination of both (54). Studies have shown that excess lactate accumulation can lead to a decrease in physiological pH that thwarts the glycolytic and force rates of skeletal muscle (55). Thus, our findings would indicate that higher lactate levels at rest may impair skeletal muscle function which could result in a reduced ΔVO_2max with endurance training.

We examined the relationship of a variety of modifiable physiological traits with ΔVO_2max within a large, diverse cohort of subjects. To our knowledge, this is one of the few studies to examine the relationship of these categories of baseline factors and VO_2max response. The strengths of the study include its large sample size and deep,

high-quality phenotyping, often including two measurements at each time point. The study, however, does have limitations to consider. The relationship between ΔVO_2max and phenotypes were only examined within one type of exercise modality. These phenotypes would need to be examined within other exercise types and dosages. Our study results may also contain potential overfitting as stepwise regression was mainly used for our statistical analysis. Lastly, a control group was not included in the HERITAGE Study and thus we do not know what the changes in VO_2max would be after 20 weeks of free living in adults.

In this post-hoc analysis of potential modifiable determinants of ΔVO_2max, we identified submaximal cardiopulmonary, resting metabolic, and body composition traits as being significant determinants of VO_2max trainability in response to endurance training. Future studies are warranted to examine the selected phenotypes and others as determinants of ΔVO_2max within different exercise doses, types, and populations.

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