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VO_2max is associated with measures of energy expenditure in sedentary condition but does not predict weight change

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Abstract

Background/Objectives—Energy expenditure measured under sedentary conditions predicts weight change but evidence that directly measured VO_2max is associated with weight change is lacking. The aim of this study was to determine the associations of VO_2max with measures of predominantly sedentary 24-h thermogenesis, and subsequent weight change.

Subjects/Methods—Three hundred fifty-seven individuals (162 females; 27 Blacks, 72 Caucasians, and 258 American Indians) had measures of body composition, resting metabolic rate (RMR), and intermittent treadmill run test for assessment of VO_2max. On a separate day, 24-h energy expenditure (EE), diet-induced thermogenesis (DIT) expressed as “awake and fed” thermogenesis (AFT), sleeping metabolic rate (SMR), and spontaneous physical activity (SPA) were measured in a whole-room indirect calorimeter. Follow-up weight for 217 individuals was available (median follow-up time, 9.5 y; mean weight change, 12.4±14.9 kg).

Results—After adjustment for fat free mass, fat mass, age, sex, and race, a higher VO_2max was associated with a higher RMR (β=68.2 kcal/day per L/min, P<0.01) and 24-h EE (β=62.2 kcal/day per L/min, P<0.05) and including additional adjustment for energy intake higher AFT (β=66.1 kcal/day per L/min, P=0.01). Neither SMR (P>0.2) nor SPA (P>0.8) were associated with VO_2max. VO_2max at baseline did not predict follow-up weight after adjustment for baseline weight, follow-up time, sex, and race (P>0.4).

Conclusion—VO_2max is associated with measures of EE including 24hEE, RMR and DIT implying a common mechanism regulating the energetics of skeletal muscle during exercise and thermogenesis. However, this did not translate to VO_2max as a predictor of weight change.

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Competing Interests: None of eclare.

Keywords

VO_2max; whole-room colorimeter; weight change; diet-induced thermogenesis; resting metabolic rate; 24-h energy expenditure

Introduction

VO_2max, the gold standard measurement of cardiorespiratory fitness (CRF), is mainly influenced by everyday physical activity (PA) [1] and heritability[2], and predicts both morbidity and mortality [3, 4]. Several studies also have shown that lower CRF, regardless of PA levels, is associated with weight gain [5, 6].This implies that VO_2max may have an independent effect on energy balance apart from the energy expenditure (EE) of PA, possibly via an effect on or through a common mechanism associated with resting metabolic rate (RMR) or the diet-induced thermogenesis (DIT).

Previous evidence for an effect of VO_2max on 24-h thermogenesis independent of PA is mixed finding no[7–10] or an inverse [11] association between VO_2max and 24-h EE. Studies using a metabolic cart have produced equally mixed results with some demonstrating a positive association of VO_2max with RMR [10, 12–18], sleeping metabolic rate (SMR) [10], and DIT [10, 14, 19–23], some showing no association with RMR [8, 22, 24–34], SMR [35, 36], or DIT [7, 9, 17, 32, 37, 38] and some studies have even shown an inverse association with these EE measures[23, 28, 39–41]. However, the sample size in all these studies have been relatively small.

While many previous longitudinal studies have reported an association between CRF and weight change[5, 42–45], most of these studies[5, 42, 43, 45] did not measure VO_2max by respiratory gas exchange as a measure of CRF. In addition, those studies did not fully control for the effect of baseline weight or adiposity on CRF and weight change, despite a known effect of adiposity itself on both the relationship between running performance and CRF[46, 47] and on weight change[48]. When baseline adiposity is adequately controlled for, CRF is not associated with weight change[49]. To further address these questions, in a cohort of Native Americans of southwestern heritage with high prevalence of obesity and measures of VO_2max and EE, we investigated the associations between VO_2max and specific measures of EE, such as RMR, SMR, DIT, and 24-h EE. We also investigated whether VO_2max predicted free-living weight change in this population over a long follow-up period.

Subjects and Methods

Subjects

Adults aged 18 to 45 years participated in a longitudinal inpatient study of risk factors for diabetes and obesity (NCT00340132). All subjects gave written informed consent before participation and any testing. Only participants who were not on medications and free of chronic or acute medical conditions with the exception of obesity and prediabetes were eligible. Eligibility was determined prior to admission to the clinical research unit, by detailed history and physical, ECG, and comprehensive blood and urine tests. After 3 days

of admission, all participants underwent a 75-gram oral glucose tolerance test to determine glucose regulation status. Individuals diagnosed with diabetes[50] were excluded from this analysis. Baseline studies were conducted between 1982 and 1992 at National Institute of Diabetes and Digestive and Kidney Diseases in Phoenix, Arizona, USA. This study was approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases.

Study protocol

Following admission to the clinical research ward, subjects were fed a weight-maintaining diet (50% carbohydrate, 30% fat, and 20% protein) based on equations for energy requirements[51]. On day 2, participant's body composition was assessed by hydrostatic underwater weighing with correction for the simultaneously measured residual lung volume[52]. After 4 days on the weight maintaining diet and following an overnight fast, RMR was measured upon awakening and then a graded exercise test for assessing VO_2max was performed. On a separate day, participants also spent 24 hours in a whole room calorimeter for measurement of 24-h EE.

VO_2max test

A graded exercise test with intermittent (discontinuous) work bouts was performed on a treadmill. Each test was started at 0 degrees elevation and involved walking at 1.5 mph. After an initial 4 min warm-up period, the elevation and speed of the treadmill were gradually increased. After 4 min at each work bout, the subject sat down until the heart rate was < 120 beats/min and they felt subjectively recovered. The test continued until the patient was subjectively exhausted, the heart rate reached 200 beats/min, or there was no further increase in the oxygen uptake. The oxygen uptake was measured during the last 30 s of each work bout. VO_2max was defined as the highest VO_2 recorded during the test. Details on expired gas collection and the analysis system used were previously described[53].

Indirect calorimetry assessment for resting metabolic rate and 24-h EE

The details of the measurements of EE and substrate oxidation by ventilated hood system [53] and in whole-body room calorimeter have been previously described [54]. Briefly, RMR was measured by ventilated hood system. After 1.5 h in supine position, a ventilated hood was placed over the subjects' head, and then expired gas was recorded continuously for an hour. For the measurement of 24-h EE, the subject entered the metabolic chamber in the morning at ~0800h after an overnight fast and stayed until the following morning. Meals were provided at 0800h, 1130h, and 1700h and an evening snack at 2000h. EE and substrate oxidation were measured continuously and calculated every 15-minute interval. EE was calculated using the formula of Lusk[55]. Spontaneous physical activity (SPA) was measured using microwave sensors. SMR was calculated averaging the EE during the nightly hours between 2330h and 0500h when SPA was <1.5%, and then extrapolated to 24 hours. The methods for the calculation of "awake and fed thermogenesis" (AFT) which includes both the DIT and the cost of arousal have been previously published[56]. Briefly, DIT is calculated as follows: 1) daytime EE is plotted versus SPA and the intercept of the regression line is calculated (EE at zero activity); 2) SMR is then subtracted from EE at zero

activity to calculate AFT. Our group has previously found that AFT predicts weight change in Native American subjects with a body mass index (BMI)>29 kg/m^2 [56].

Longitudinal analyses for weight change and body composition.

Follow-up data on body composition was obtained from participants who returned for repeated admissions in the above described study. Body composition at follow-up was determined by underwater weighing or dual energy x-ray absorptiometry with percent fat regressed to original hydrostatic weight values [57].

For follow-up analyses of body weight, Native American participants of southwestern heritage also participated in a longitudinal study of health between 1965–2007 (NCT00339482). In this study, participants were invited for outpatient visits approximately every 2 years regardless of health status. At these visits participants came in fasting, underwent 75-gram oral glucose tolerance test and had measures of weight and height. Follow-up weights were collected at the last available follow-up visit or last visit prior to development of diabetes.

Statistical analyses

Prior to analyses, all variables were tested for normal distribution by sex based on kurtosis and skewness. Non-normally distributed variables were log transformed. The unpaired T-test was used to test for differences in variables by sex. Associations of VO_2max with measures of body composition and age were analyzed using general linear models. General linear models were also used to investigate the associations of VO_2max with EE measures, or follow-up weight, with adjustments for covariates. For all models, inclusion of variables was based on previous knowledge of these variables as confounders. Pearson's correlation coefficient was also used to investigate the associations of VO_2max with rate of weight change and for the associations between changes in VO2max and changes in body composition. An interaction term for sex*VO_2max was tested in models of follow-up weight and weight change. When the interaction term was significant, analyses was performed separately by sex. All statistical analyses were performed by SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA). P value was considered significant if < 0.05. Data are presented as mean ± SD.

Results

Subject characteristics

Baselines measures of body composition and EE are shown in Table 1. Three hundred fifty-seven individuals without diabetes had measures of anthropometry tests and VO_2max. Of the 357 individuals, 207 individuals had measures of 24-h EE and 162 individuals of these 207 individuals had measures of RMR. As expected, BMI, fat mass (FM), and %FM were significantly higher in females than in males. By contrast, body weight, FFM, VO_2max, RMR, SMR, and 24-h EE were significantly higher in males.

Associations of VO_2max with body composition and age

In linear models adjusting for sex, VO_2max was positively correlated with body weight (β = 10.0 mL per kg, $P < 0.0001$), FFM (β = 27.9 mL per kg, $P < 0.001$; Figure1A), FM (β = 12.1 mL per kg, $P < 0.0001$), %FM (β = 12.3 mL per %, $P = 0.02$; Figure1B), and BMI (β = 21.0 mL per kg/m^2, $P < 0.0001$; Figure1C). Sex remained a significant predictor of VO_2max in the above models. There was no interaction by sex and above variables on VO_2max. In models adjusted for sex, FFM, and FM, VO_2max was negatively associated with age (β = −12.6 mL per year, $P < 0.001$; Figure1D) but there was no interaction between sex and age on VO_2max ($P > 0.1$). In models adjusted for age, sex, FFM, and FM there was no difference in VO_2max by race ($P > 0.3$). The model prediction for VO_2max based on FFM, FM, age, and sex was as follows ($R^2 = 0.730$, adjusted $R^2 = 0.727$):

$$VO2\text{max}(mL/min) = 36.8 \times FFM(kg) - 9.6 \times FM(kg) - 12.6 \times age(years) + 610.9(if\ male) + 915.4$$

VO_2max and EE measures

Figure 2 and Table 2 show the associations between adjusted VO_2max and adjusted EE measures. VO_2max and all EE measures were adjusted for FFM, FM, age, sex, and race while 24-h RQ was adjusted for %FM, age, sex, energy balance, and race. VO_2max was positively associated with RMR (Standardized $\beta = 0.214$, $P < 0.01$; Figure 2D), AFT (Standardized $\beta = 0.194$, $P = 0.015$; Figure 2B), and 24-h EE (Standardized $\beta = 0.147$, $P < 0.05$; Figure 2A), but not with SMR ($P > 0.2$; Figure 2C), SPA ($P > 0.8$; Figure 2E), or 24-h RQ ($P > 0.4$; Figure 2F). Time from admission to EE assessments was not associated with residuals of RMR, AFT, and 24-h EE in any of the adjusted models (All $P > 0.1$).

VO_2max and subsequent body composition and weight change

Participants with baseline and follow-up data for both VO_2max and body composition (n =135, 55 females) are shown in (Table 3). The average weight change was 6.1 ± 11.2 kg over a median follow-up of 4.4 years (IQR: 2.6–6.5 years). In this group, baseline VO_2max did not predict follow-up FFM ($P > 0.3$) or FM ($P > 0.3$) when adjusted for baseline FFM, FM, age, sex, and follow-up time. Changes in VO_2max were not correlated with changes in weight ($P > 0.9$), FFM ($P > 0.3$), or FM ($P > 0.5$).

Of the 357 individuals, 217 (97 females) had available follow-up weight data (Table 3). The baseline characteristics of these 217 individuals did not differ from entire cohort. Mean weight change was 12.4 ± 14.9 kg over a median follow-up time of 9.5 years (IQR: 5.5–17.0 years). Nether VO_2max ($P > 0.8$, Figure 3A) nor VO_2max divided by baseline FFM ($P > 0.7$, Figure 3B) were associated with the rate of weight change (%/year). VO_2max did not predict follow-up weight after adjustment for baseline weight, age, sex, and follow-up time as covariates ($P > 0.4$) or change in weight after adjustment for sex, age, and follow-up time ($P > 0.1$). Similar results were found when VO_2max was divided by baseline FFM ($P > 0.5$). On the other hand, RMR inversely predicted follow-up weight (Standardized $\beta = -0.175$, $P = 0.013$, $N = 206$) after adjustment for baseline weight, sex, age, and follow-up time and change in weight (Standardized $\beta = -0.159$, $P = 0.023$, $N = 206$) after adjustment for sex, age, and follow-up time.

Discussion

In a large cohort including Native Americans of southwestern heritage in whom measures of EE including RMR, 24-h EE and AFT predict weight change, we found that VO_2max is associated with RMR, 24-h EE and AFT. However, this did not translate into an effect of VO_2max on subsequent weight or body composition change, even though in this cohort we found that lower RMR was associated with higher weight gain in Native Americans as previously reported [58].

Previous studies have examined whether VO_2max is associated with EE and/or weight change. These studies have shown mixed results. In terms of the association of VO_2max with EE, most of the previous studies did not have complete or gold standard measures of EE, as we did in this study. In fact, we had measures of EE on 2 separate occasions (24-h EE as measured in our whole room calorimeter and RMR measured on a separate day using a ventilated hood system), and we demonstrated positive associations of VO_2max with EE for both measures. Moreover, our measure of DIT (which we term AFT), but not sleeping EE, was also associated with VO_2max.The only previous study with a relatively large sample size (n=78) and similar measures did not find significant associations between VO_2max and 24-h EE, RMR, or DIT [7].

Despite these associations with EE, VO_2max did not predict free-living weight change in this Native American population. Many previous longitudinal studies have demonstrated a protective effect of CRF on weight management[5, 42–45]. However, CRF was assessed differently across studies, and none has used indirect calorimetry during exercise along with appropriate measures of body composition to adjust for confounders. Because our study measured actual VO_2max by expired gas during exercise at maximum effort, we were able to run the longitudinal analyses for weight change based on VO_2max and body composition independently. To the extent that VO_2max represents PA and CRF, our result is consistent with the conclusion of a recent systematic review which reported that PA does not strongly affect weight or fat gain[59].

For every 1 L of VO_2max increase, there was an associated increase in daily EE by approximately 60 kcal. This increased EE is comparatively small when compared with total absolute EE (≈ < 3% of 24-h EE). However, the interindividual variability in VO_2max after adjusting body composition, sex, age, and race still ranged from –1.1–1.4L; this translates to a 156 kcal difference in EE (2.7×62.2 kcal/day) between individuals with relatively higher and lower VO_2max. This is on par with the EE difference which in our previous studies has accounted for weight gain in this population (a 100 kcal decrease in EE was associated with a 0.2kg/y weight gain)[60]. In addition, as it has been suggested by Hill et al.[61, 62], that a daily EE difference of less than 1% is sufficient to predispose to weight gain. Our data indicates that variability in VO_2max however is not a determinant of weight change.

Whether a common mechanisms might underlie associations between VO_2max and measures of EE, especially DIT, remains unclear. Skeletal muscle mitochondrial content and function share common associations between VO_2max and EE. Consistent with our findings, in humans, mitochondrial density and respiration in the vastus lateralis correlates with

VO_2max, RMR, and glucose and insulin-induced thermogenesis during insulin clamp[63]. Adrenergic tone affects blood volume distribution and delivery in upright versus supine positions which might explain the association between VO_2max and 24hEE but the lack of association with SMR [64]. Several lines of evidence indicate a common mechanism between VO_2max and DIT. Exercising and sedentary adults have differences in the β-adrenergic thermic response which contributes to the variation in DIT between these individuals[38]. Postprandial gut hormone responses may also link VO_2max and DIT. Regular exercise training leads to higher post-meal GLP-1 and PYY concentrations and higher GLP and PYY response to meal is associated with higher postprandial thermogenesis albeit following Roux-en-Y gastric bypass or vertical banded gastroplasty[65]. VO_2max is also correlated with short-chain fatty acids production via fermentation[66]. Short-chain fatty acids act on colonic enteroendocrine L cells and promote GLP-1 and PYY secretion[67]. Thus, there is evidence for a possible common mechanism explaining these associations.

One possible explanation why VO_2max was not a predictor of weight change despite its association with EE may be the mediating effect of exercise. A review including several studies using doubly labeled water for assessment of EE concluded that exercise-induced increases in EE resulted in increased food intake[68]. Thus, greater fitness, as influenced by regular PA and resulting in higher VO_2max, may increase energy intake opposing any favorable effect on daily EE. However, even if regular PA does not result in weight loss or maintaining weight, it should be noted that regular PA has several other benefits for health. For example, a recent exercise intervention study showed that 4-weeks of exercise training did not lead to weight loss but lowered intrahepatic lipid content [69].

Our study has several strengths. We had measures of body composition, allowing appropriate adjustment for confounders for both EE and VO_2max. Also, we had two separate measures of EE. One assessed using the gold standard method over 24 h in a whole room calorimeter and RMR using a metabolic cart performed on a separate day. We also had a large sample size with follow-up of both weight and body composition. In terms of confounding factors, most previous studies divide VO_2max by FFM. As shown in Figure 1, the intercept of the association between VO_2max and FFM was different from zero, indicating the need to use multiple regression analysis, as we did, for the proper adjustment of VO_2max and for comparing the interindividual difference among individuals of varying body size.

We acknowledge our study has also some limitations. First, we were unable to explore potential physiological mechanisms underlying the association between the VO_2max and EE measures. Second, those with follow-up measures of weight and body composition were fewer than the overall cohort and were only Native American. This, somewhat limits the overall power and the generalizability of our findings.

In conclusion, higher VO_2max was associated with greater 24-h EE, greater AFT and higher RMR. Although every 1 L of VO_2max was associated on average with increased daily EE by 60 kcal, we did not see an effect of VO_2max on long-term weight change. Thus, VO_2max and 24-h EE and DIT may share common mechanisms, however any protective effect of

higher VO_2max on weight gain appears to be limited. Thus, training to improve VO_2max as a method to prevent weight gain or promote weight loss may not be an effective weight management strategy.

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Abbreviations:

AFT	awake and fed thermogenesis
BMI	body mass index
CRF	cardiorespiratory fitness
DIT	diet-induced thermogenesis
EE	energy expenditure
FFM	fat free mass
FM	fat mass
PA	physical activity
RMR	resting metabolic rate
RQ	respiratory quotient
SMR	sleeping metabolic rate
SPA	spontaneous physical activity

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Highlights:

- Higher VO_2max was associated with greater 24-h energy expenditure (EE).
- Every 1 L of VO_2max was associated with increased daily EE by 60 kcal.
- VO_2max does not predict weight change in American Indians of southwestern heritage.

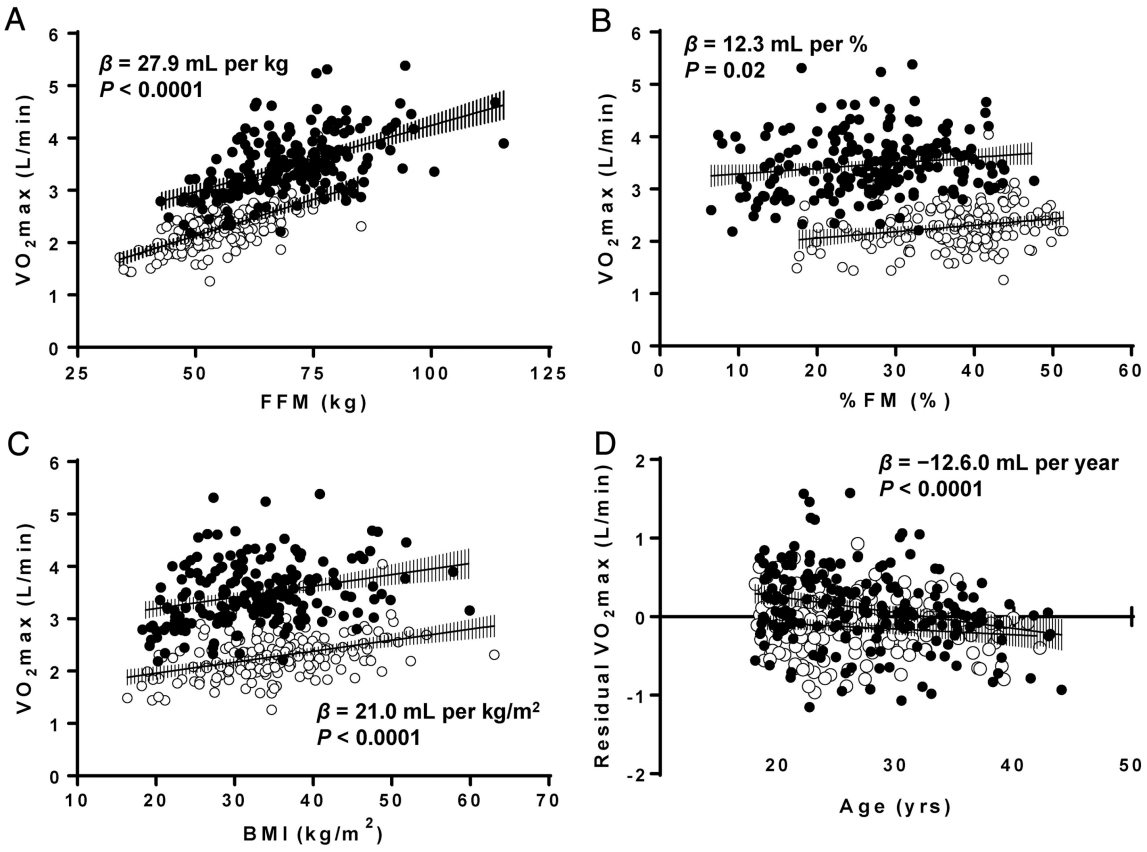

Figure 1-

Association of VO_2max with measures of body compositions and age in females (open circles) and males (closed circles). (A) VO_2max versus fat free mass. (B) VO_2max versus % fat. (C) VO_2max versus body mass index. (D) VO_2max, adjusted for fat free mass and fat mass versus age. BMI, body mass index; FFM, fat free mass; FM, fat mass. Error bars show 95% confidence intervals.

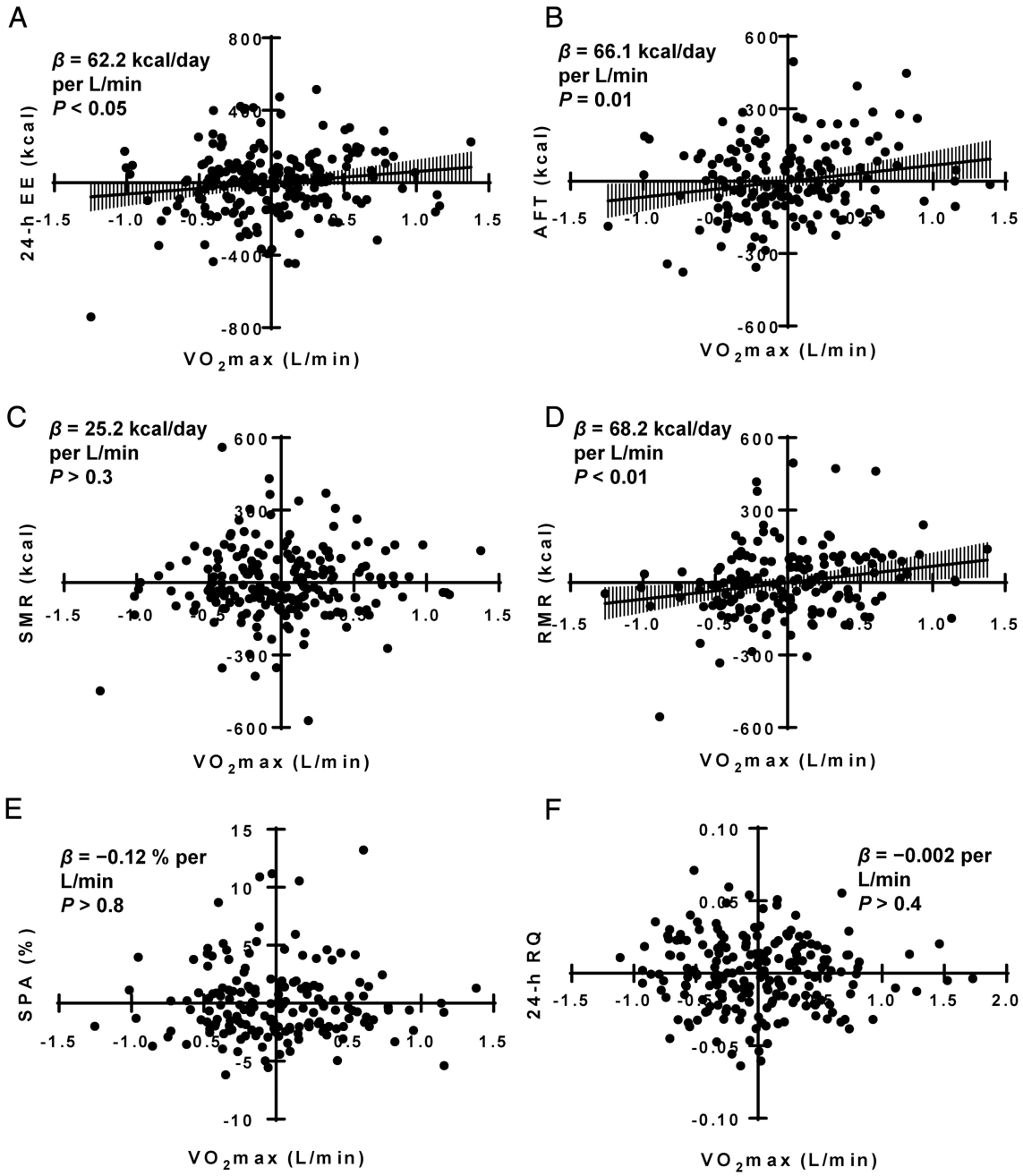

Figure 2-

Associations of VO_2max with measures of EE. (A) Residuals for VO_2max versus residuals 24-h energy expenditure (B) Residuals for VO_2max versus residuals awake and fed thermogenesis (C) Residuals for VO_2max versus residuals for sleeping metabolic rate (D) Residuals for VO_2max versus residuals for resting metabolic rate. (E) Residuals for VO_2max versus residuals for spontaneous physical activity (F) Residuals for VO_2max versus residuals 24-h RQ. VO_2max, 24-h EE, AFT, SMR, RMR and SPA were all adjusted for age, sex, race, fat free mass, fat mass. AFT additionally adjusted for energy balance. RQ adjusted for age, sex race, %fat and energy balance. AFT, awake and fed thermogenesis; EE, energy

expenditure; RMR, resting metabolic rate; RQ, respiratory quotient; SMR, sleeping metabolic rate; SPA, spontaneous physical activity. Error bars show 95% confidence intervals.

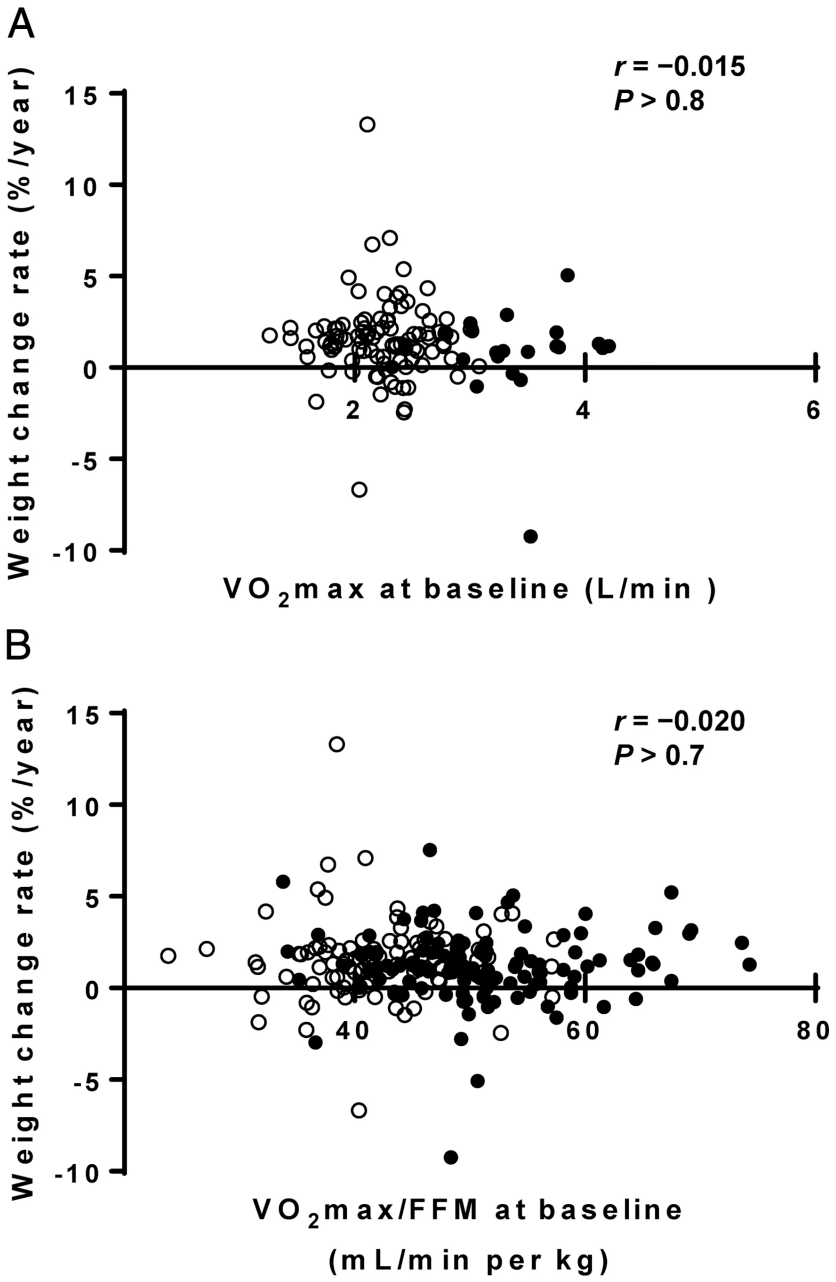

Figure 3-

Associations between VO_2max versus weight change rate. (A) Baseline VO_2max versus weight change rate. (B) Baseline VO_2max/FFM versus weight change rate. Open circles, females; closed circles, males.

Table 1

Subjects characteristics.

Variables	Mean ± SD	Range (min-max)
N (women, %)	357 (162,45.4%)	
Race (number)	Black = 27, Caucasian = 72, American Indian = 258 (Full heritage American Indians of southwestern heritage = 249)	
Age (years)	26.8 ± 6.1	18.1–44.0
Body mass index (kg/m^2)	33.74 ± 8.23	16.34–63.06
Weight (kg)	94.3 ± 24.4	41.2–181.1
Fat free mass (kg)	63.0 ± 13.1	33.9–115.4
Fat mass (kg)	31.3 ± 15.2	4.0–84.5
% fat mass (%)	31.7 ± 9.9	6.5–51.3
VO_2max (L/min)	2.927 ± 0.783	1.263–5.381
Residual VO_2max (mL/min) *	4.414×10^{-13} ±406.7	-1176–1491
Resting metabolic rate (kcal/day, *N* = 162)	1815 ± 297	1097 – 2641
Sleep metabolic rate (kcal/day, *N* = 202)	1665 ± 293	994–2484
Awake and fed thermogenesis (kcal/day, *N* = 165)	424 ± 168	88–926
Spontaneous physical activity (%, *N* = 173)	9.5 ± 3.3	3.1–22.8
24-h energy expenditure (kcal, *N* = 207)	2330 ± 406	1412–3651
24-h RQ(N = 207)	0.852 ± 0.027	0.776–0.929

* Residual VO2max was obtained by a model including fat-free mass, fat mass, age, and sex as independent variables.

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Table 2.

Results for the associations between VO_2max and EE measures using general linear models.

Dependent variables	β	Standardized β	P- value	95% confidence limits	R^2 for model
Resting metabolic rate (kcal/day, N=162)	68.2 ± 25.0	0.214	0.007	18.8–117.7	0.780
Sleep metabolic rate (kcal/day, N=202)	27.4 ± 24.3	0.081	>0.2	−20.6–75.3	0.753
Awake and fed thermogenesis (kcal, N=165)	66.1 ± 26.9	0.194	0.015	13.0–119.2	0.214
Spontaneous physical activity (%, N=173)	−0.11± 0.55	−0.016	>0.8	−1.2–1.0	0.127
24-h energy expenditure (kcal, N=207)	62.2 ± 29.6	0.147	<0.05	3.9–120.5	0.807
24-h RQ (N=207)	−0.003 ± 0.003	−0.055	>0.4	−0.009–0.004	0.225

B, Standardized β, P-value, and 95% confidence limits represent the results for VO_2max as independent variable of general linear models. Other covariates as independent variables for all EE measures were fat-free mass, fat mass, age, sex, and race, and for 24-hRQ were %fat mass, energy balance, age, sex, and race.

Table 3.

Subject characteristics for follow-up analyses.

Variables	Females			Males			P value for sex difference	P value for sex interaction
	Baseline	Follow up	Δ (P value)	Baseline	Follow up	Δ (P value)		
Study 1: delta VO_2max vs. delta body composition								
N (number)	55			80				
Race (number)	Full heritage American Indians of southwestern heritage = 55			Full heritage American Indians of southwestern heritage = 77, other Indians = 3			> 0.1	
Age (years)	25.7 ± 5.7	29.7 ± 6.3	4.0 ± 2.3	25.9 ± 5.7	30.7 ± 5.6	4.8 ± 2.2	0.043	0.094
Body mass index (kg/m^2)	36.60 ± 6.52	38.24 ± 7.08	1.64 ± 3.35 (< 0.001)	33.81 ± 8.30	36.35 ± 9.50	2.54 ± 4.17 (< 0.0001)	> 0.6	> 0.4
Body weight (kg)	92.9 ± 18.6	97.1 ± 20.0	4.2 ± 8.4 (< 0.001)	99.0 ± 27.2	106.4 ± 31.5	7.4 ± 12.7 (< 0.0001)	> 0.5	> 0.3
Fat free mass (kg)	55.1 ± 8.6	57.0 ± 8.9	1.9 ± 3.9 (< 0.001)	68.5 ± 12.5	72.0 ± 13.8	3.5 ± 6.1 (< 0.0001)	> 0.6	> 0.4
Fat mass (kg)	37.8 ± 11.6	40.0 ± 12.0	2.3 ± 6.8 (= 0.016)	30.5 ± 16.0	34.6 ± 18.5	4.1 ± 8.7 (< 0.001)	> 0.3	> 0.1
% fat mass (%)	39.9 ± 5.9	40.5 ± 4.6	0.7 ± 4.3 (> 0.2)	28.7 ± 9.0	30.5 ± 7.8	1.8 ± 5.2 (< 0.01)	0.030	> 0.1
VO_2max (mL/min)	2280.9 ± 357.1	2332.2 ± 443.0	51.3 ± 338.7 (> 0.2)	3421.4 ± 525.4	3462.6 ± 696.3	41.2 ± 562.2 (> 0.5)	> 0.6	> 0.9
Study 2: VO_2max vs. weight change								
N (number)	97			120				
Race (number)	Full heritage American Indians of southwestern heritage = 97			Full heritage American Indians of southwestern heritage = 114, other Indians = 6			0.026	
Age (years)	25.1 ± 5.5	36.4 ± 8.1	11.3 ± 6.8	26.2 ± 5.9	37.3 ± 7.9	11.1 ± 6.9	> 0.5	> 0.5
Body mass index (kg/m^2)	35.17 ± 7.49	39.75 ± 8.59	4.58 ± 5.32 (< 0.0001)	32.69 ± 8.19	36.79 ± 10.44	4.10 ± 5.28 (< 0.0001)	0.028	0.033
Body weight (kg)	89.2 ± 20.4	101.5 ± 22.9	12.3 ± 13.6 (< 0.0001)	95.6 ± 26.4	108.1 ± 33.3	12.5 ± 15.9 (< 0.0001)	0.025	0.021

The differences between baseline and follow up were analyzed by pared t-test. A probability of sex difference in the frequency of Full heritage American Indians of southwestern heritage was analyzed by Chi-Square test. A probability of sex difference or sex interaction was analyzed by general linear model.