Supplemental Table 1 Exercise Training and Activity Levels

	OW-Trained	
Aerobic Training	*M*	*F*
Adherence, %	90 ± 5	83 ± 8
Prescribed minutes/week	127 ± 4	166 ± 10
Actual minutes/week	107 ± 6	123 ± 10
Frequency, sessions/week	2.5 ± 0.2	2.5 ± 0.3
Resistance Training	*M*	*F*
Adherence, %	86 ± 4	76 ± 10
Prescribed sets/week	72	72
Actual sets/week	60 ± 3	54 ± 7
Frequency, sessions/week	2.6 ± 0.1	2.3 ± 0.2
Baseline Activity Level	**OW-Untrained (N)**	
Active 1-2 days per week	6	
Active 3-4 days per week	1[a]	
Active every day	0	
No regular activity	6	
Baseline Activity Level	**Control (N)**	
Active 1-2 days per week	0	
Active 3-4 days per week	8	
Active every day	1	
No regular activity	1	

[a]Walking

Supplemental Table 2 Additional hormones, cytokines and conventional metabolites

	Control	OW-Untrained	OW-Trained
Hormones and Cytokines in Plasma	*n = 10*	*n = 13*	*n = 9*
IL-1b (pg/mL)	0.20 ± 0.05	0.12 ± 0.02	0.16 ± 0.02
IL-6 (pg/mL)	1.19 ± 0.27	1.23 ± 0.11	1.16 ± 0.17
IL-8 (pg/mL)	7.7 ± 0.9	7.7 ± 0.8	7.6 ± 0.8
IGFBP3 (ng/mL)	1.94 ± 0.10	2.03 ± 0.97	2.01 ± 0.14
Resistin (ng/mL)	3.9 ± 0.3	3.9 ± 0.4	3.7 ± 0.5
Ghrelin (pg/mL)	570 ± 96	470 ± 92	394 ± 104
PYY (pg/mL)	117 ± 10	88 ± 11	92 ± 13
AgRP (pg/mL)	64 ± 9	67 ± 5	64 ± 6
Cortisol (nmol/L)	751 ± 55	710 ± 62	639 ± 69
RBP4 ($\mu g/mL^{-1}$)	32.9 ± 3.8	40.1 ± 2.6	36.2 ± 2.7
Conventional Metabolites in Plasma			
HDL cholesterol (mmol/L)	1.33 ± 0.14	0.98 ± 0.08	0.99 ± 0.06
LDL cholesterol (mmol/L)	2.64 ± 0.21	3.00 ± 0.15	3.03 ± 0.27
Uric acid (µmol/L)	287 ± 23	386 ± 21	358 ± 25
Creatinine (µmol/L)	61.5 ± 4.0	71.0 ± 4.8	66.9 ± 4.3
Albumin (g/L)	38.9 ± 0.6	39.0 ± 0.5	38.3 ± 0.5

Values are mean ± SEM. $\alpha = 0.01$. IL: interleukin; IGFBP3: insulin-like growth factor-binding protein 3; PYY: peptide YY (tyrosine tyrosine); AgRP: Agouti-related protein; RBP4: retinol binding protein 4; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Supplemental Table 3 Principal Components Analysis: Individual components of factors*

Group/Name	Individual Components	Factor Load
Plasma BCAA-related	Leu/Ile	0.909
	Val	0.883
	Phe	0.869
	Glx	0.790
	Tyr	0.720
	Pro	0.440
	Gly	-0.664
Plasma hormones and	Leptin	0.834
conventional metabolites	hsCRP	0.828
	Pyruvate	0.752
	GIP	0.720
	Lactate	0.538
Muscle medium/long-chain AC	C14	0.971
	C16:1	0.961
	C12	0.951
	C14:1	0.949
	C16	0.938
	C18:1	0.933
	C14:2	0.933
	C6	0.924
	C18:2	0.916
	C8	0.896
	C18	0.885
	C10	0.858
	C8:1	0.748
	C4/Ci4	0.611

*Factor load > 0.40. BCAA: branched-chain amino acid; AC: acylcarnitines; hsCRP: high-sensitivity C-reactive protein; GIP: glucose-dependent insulinotropic peptide.

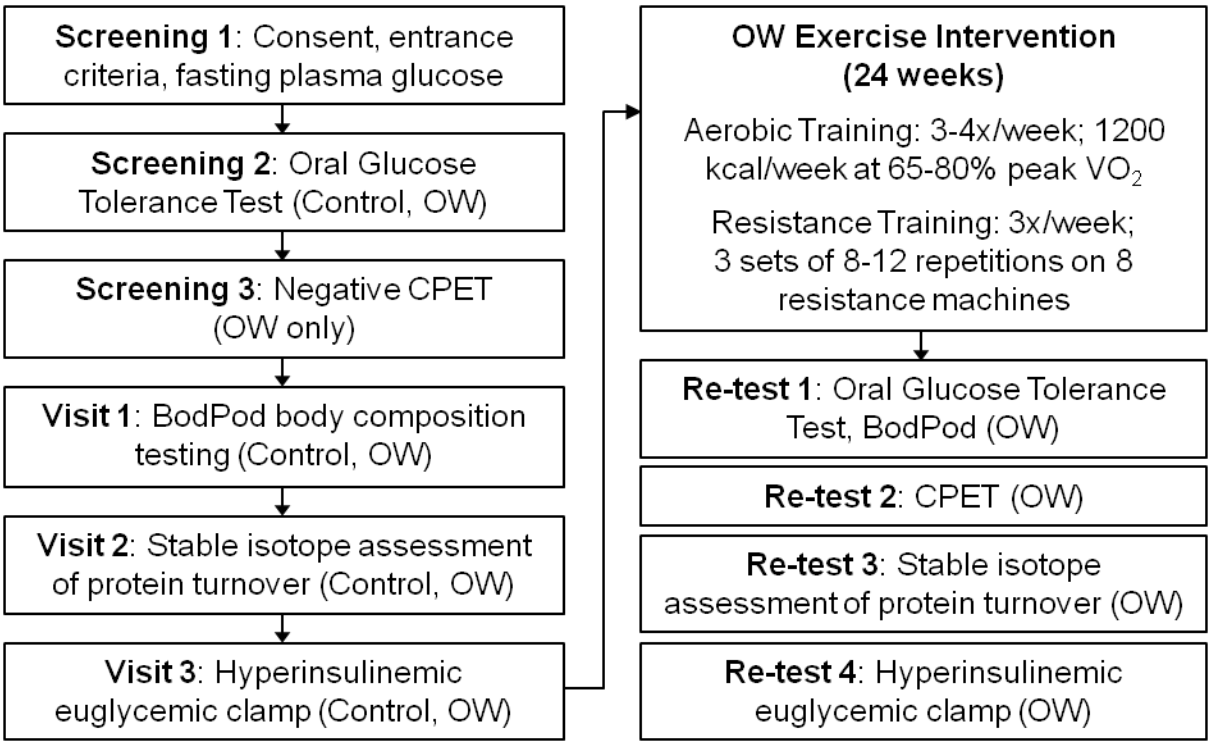
Supplemental Table 4 Pearson Correlation Coefficients: metabolites and insulin sensitivity

				R value	
Metabolite group or factor:	**Control**	**OW-Untrained**	**OW-Trained**	**HOMA-IR**	**GIR**
Plasma:	*Group Mean ± SEM*				
BCAA-related factor	-1.06 ± 0.11	0.50 ± 0.23	0.46 ± 0.25	0.677[a†]	-0.677[a†]
CM factor	-0.95 ± 0.19	0.67 ± 0.21	0.25 ± 0.23	0.589*	-0.761*
Sum Ile, Phe, Tyr (μM)	168 ± 6	210 ± 11	202 ± 6	0.708*	-0.775*
Sum α-keto acids (μM)	66 ± 3	85 ± 3	76 ± 4	0.628*	-0.759*
Sum BCAA (μM)	400 ± 15	459 ± 25	446 ± 21	0.449‡	-0.600*
Muscle:					
MC, LC AC factor	-0.48 ± 0.22	0.24 ± 0.32	0.24 ± 0.38	0.386‡	-0.356
Sum C8-18 AC (μM)	0.24 ± 0.06	0.54 ± 0.11	0.49 ± 0.09	0.441[a†]	-0.442[a†]
Protein Turnover [b]:					
Endogenous Leu R_a	1.95 ± 0.06	2.41 ± 0.07	2.51 ± 0.10	0.409	-0.582
Leu oxidation	0.27 ± 0.01	0.39 ± 0.03	0.37 ± 0.03	0.299	-0.474
NOLD	1.76 ± 0.06	2.10 ± 0.05	2.22 ± 0.08	0.404	-0.558
FSR (%•h^{-1})	0.032 ± 0.004	0.029 ± 0.005	0.047 ± 0.003	-0.071	0.000
Delta Scores	**(OW-Untrained) – (OW-Trained)**		**Min, Max**	**ΔHOMA-IR**	**ΔGIR**
Plasma:					
Δ Sum BCAA	13.1 ± 20.2		-65, 116	-0.389	-0.801†
Δ Sum α-keto acids	8.9 ± 3.8		-13, 25	-0.369	-0.394
Muscle:					
Δ Sum C8-18 AC	0.13 ± 0.13		-0.39, 0.61	0.426	0.648
Protein Turnover:					
Δ Endogenous Leu R_a	-0.102 ± 0.120		-0.912, 0.460	0.157	0.264
Δ Leu oxidation	0.019 ± 0.042		-0.167, 0.137	0.472	-0.075
Δ NOLD	-0.121 ± 0.095		-0.766, 0.221	-0.008	0.366

Δ FSR (%•h^{-1})	-0.025 ± 0.016	-0.096, 0.051	-0.032	0.022

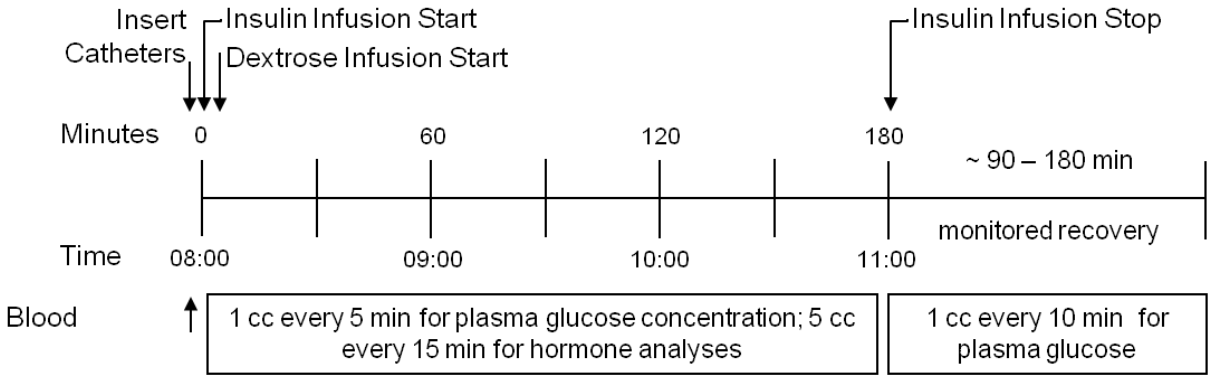
GIR: glucose infusion rate during hyperinsulinemic euglycemic clamp; BCAA: branched-chain amino acid; CM: conventional metabolite; MC: medium-chain; LC: long-chain; AC: acylcarnitine; R_a: rate of appearance; NOLD: non-oxidative leucine disposal; FSR: fractional synthesis rate. [a] Spearman correlation coefficient for non-normally distributed variables. [b] Leu Ra, oxidation and NOLD are expressed in μmol (kg FFM^{-1}) min^{-1}. * $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$.

Supplemental Figure 1



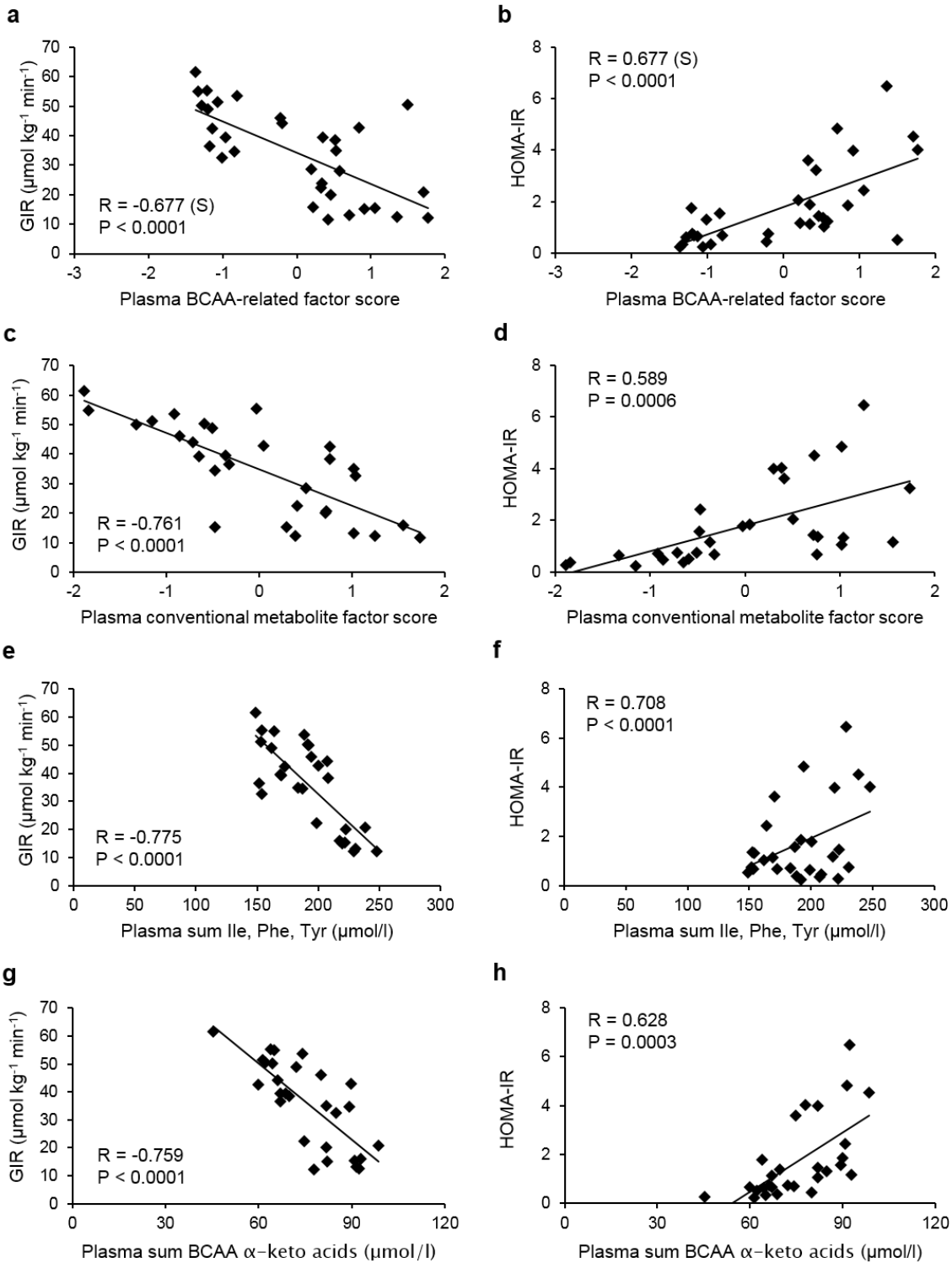
Supplemental Figure 1: Study Design. At Screening 1, subjects were informed about the study and provided their written consent to participate. Subjects who met all inclusion criteria at Screening 1 returned for an oral glucose tolerance test (Screening 2). Control subjects who met all criteria in Screenings 1 and 2 were enrolled in the study. Overweight (OW) subjects who met all criteria in Screenings 1 and 2 underwent a cardiopulmonary exercise test (CPET, Screening 3). All qualified subjects then participated in 3 study visits as shown. Following completion of Visits 1-3, OW subjects participated in a 24 week aerobic + resistance exercise training program. On completion of the training program, OW subjects were re-tested (OW-Trained) to compare with Baseline measures (OW-Untrained). Re-tests 1, 3, and 4 were scheduled 24-36 hours after the previous exercise session.

Supplemental Figure 2



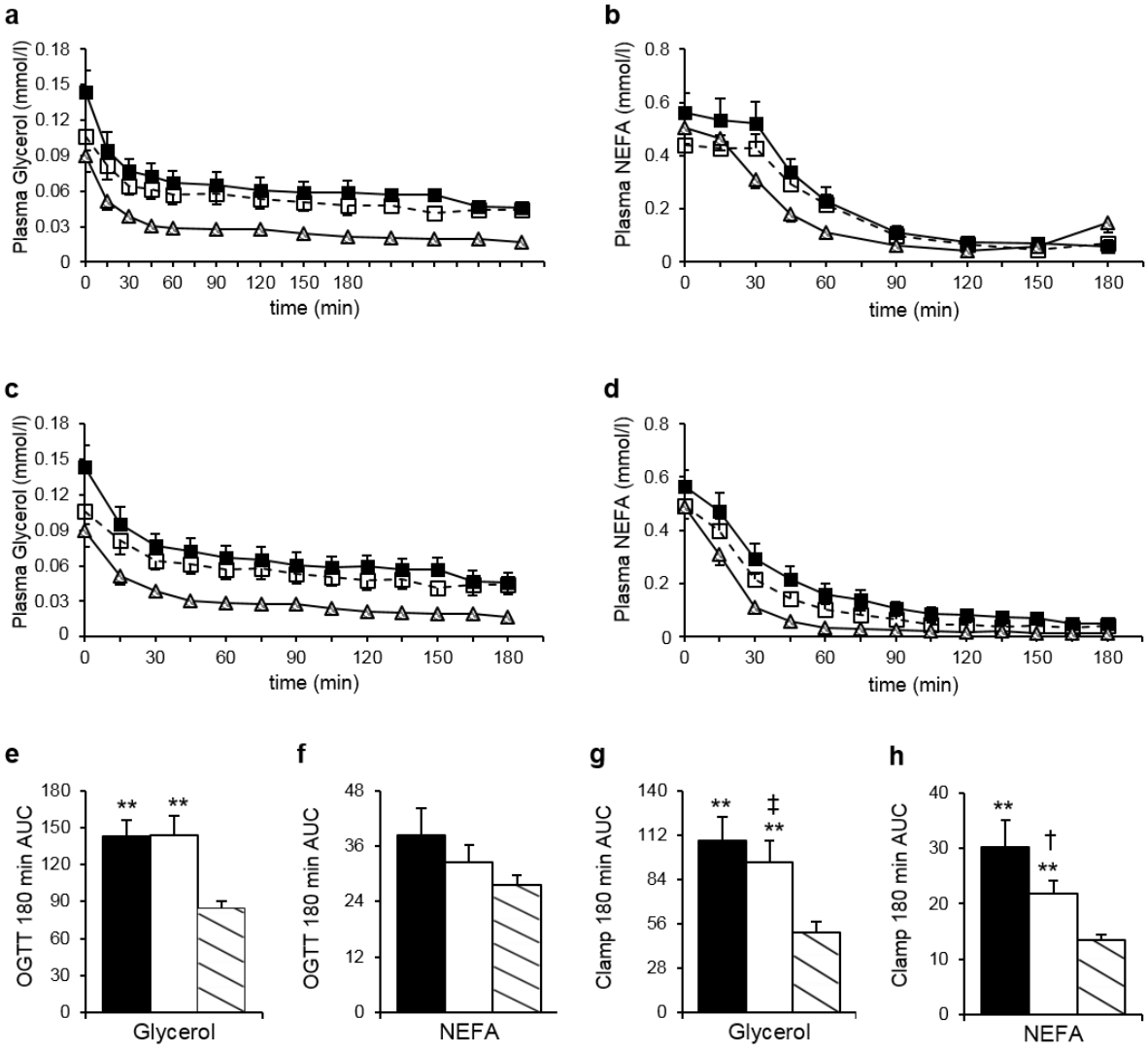
Supplemental Figure 2: Protocol design for hyperinsulinemic euglycemic clamp. A background blood sample was obtained (arrow) prior to the start of a primed, constant insulin infusion (40 mU • (m^2 body surface area)$^{-1}$ · min^{-1}). A 20% dextrose infusion was begun 4 min after start of insulin infusion. Rate of dextrose infusion was variably adjusted based on 5 minute plasma glucose measures with a goal plasma glucose of 100 mg•dL^{-1}.

Supplemental Figure 3



Supplemental Figure 3: Plasma metabolite relationships with measures of insulin sensitivity. See Supplemental Table 3 for Pearson or Spearman (S) correlations.

Supplemental Figure 4



Supplemental Figure 4: Plasma glycerol and NEFA concentrations during OGTT and Hyperinsulinemic-euglycemic clamp. OW-Untrained = black squares and bars; OW-Trained = white squares and bars; Control = triangles and striped bars. Plasma glycerol (A) and NEFA (B) concentrations during oral glucose tolerance test. Plasma glycerol (C) and NEFA (D) concentrations during clamp. Areas under the curve for OGTT glycerol (E) and NEFA (F), and clamp glycerol (G) and NEFA (H). AUCs calculated from mg/dL values for glycerol. * $p < 0.05$ versus Control; ** $p < 0.01$ versus Control; † $p < 0.05$ versus OW-Untrained; ‡ $p < 0.01$ versus OW-Untrained. Values are mean ± SEM. n = 9 OW groups, n = 10 Control.

Supplemental Methods:

This trial was listed on clinicaltrials.gov (Identifier: NCT01786941).

Participants. Main inclusion criteria for both groups were age 40-65 years, stable medication use, and stable weight for previous 6 months. Subjects were excluded if they had a history of diabetes or heart disease, uncontrolled hypertension, orthopedic limitations, were taking medications for diabetes or heart disease, pregnant or intending to become pregnant, or used tobacco or medications known to affect carbohydrate or lipid metabolism. Additional criteria for Control included body mass index (BMI) 18.0-24.9, and for OW included BMI 25.0-35.4, and inactive (exercise less than 2 days/week). OW subjects underwent a cardiopulmonary exercise test (CPET) to determine cardiorespiratory fitness (rVO_2) and ensure they were healthy enough to perform exercise [1]. Additional inclusion/exclusion criteria can be found on clinicaltrials.gov (Identifier NCT01786941).

Protein turnover. The evening prior to the study, subjects were fed a standard dinner (46 kJ (11 kcal)/kg fat free mass (FFM); 60% carbohydrate, 20% fat, 20% protein) between 18:00 and 19:00, prepared by a metabolic nutritionist. Subjects returned at 08:00, following an overnight fast.

Tracer doses were as follows: ^{13}C bicarbonate priming dose = 1.2 μmol•kg^{-1}; 1-^{13}C leucine priming dose = 4.8 μmol•kg^{-1}, infusion rate = 0.08 μmol•kg^{-1}•min^{-1}; ring-D_5-phenylalaine priming dose = 2 μmol•kg^{-1}, infusion rate = 0.05 μmol•kg^{-1}•min^{-1}; Cambridge Isotopes, Tewksbury, MA. For α-KIC, plasma samples were deproteinized with ice-cold acetone and lipids were extracted with hexane. The aqueous fraction was dried, derivatized with 1:1 N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA) and acetonitrile and analyzed by GC/MS monitoring ions *m/z* 301/302. For leucine and phenylalanine, plasma was collected in

10% sulfosalicylic acid. Supernatants were run on cation exchange columns (Bio-Rad Laboratories; Richmond, CA), eluted with NH_4OH, dried, derivatized and analyzed by GC/MS monitoring ions 302/303/305 (leucine, internal standard (5,5,5,-D_3)) and 336/337/341 (phenylalanine, internal standard ^{15}N).

Nutrition assessments. Subjects were instructed to not alter their diet over the course of the study. At baseline, all subjects completed a 24-hour dietary recall with a nutritionist, as well as a 3-day dietary record. Instructions for completing the 3-day record were given by a nutritionist, and included completing the record over 2 week days and 1 weekend day. OW subjects participating in the exercise intervention supplied 24-hour dietary recalls once a month with the nutritionist, and completed 3-day dietary records at 3- and 6-months of intervention.

Hyperinsulinemic-euglycemic clamp. Following an overnight fast (minimum 12 hours), subjects arrived at 08:00 and catheters were inserted into an antecubital vein for insulin (Humulin R; Lilly USA; Indianapolis, IN) and dextrose (20% dextrose injection; Hospira, Inc.; Lake Forest, IL) infusion, and in a vein of the opposite hand for arterialized blood sampling. Background blood samples were collected, and a primed, continuous infusion of insulin (40 mU•(m^2 body surface area)$^{-1}$•min^{-1}) was begun and continued from 0 to ~180 min. Euglycemia (plasma glucose concentration ~5.55 mmol/L) was maintained by variable infusion of a 20% dextrose solution, based on 5 min measurements of plasma glucose concentrations using a YSI Glucose/Lactate analyzer (Yellow Springs, OH). Additional blood samples were collected every 15 min for substrate and hormone measurements. Hepatic glucose production is suppressed by >85-90% in lean and obese non-diabetic individuals during insulin infusion at 40 mU m^{-2} min^{-1} [2]. Therefore, exogenous glucose infusion rate (GIR) approximates the rate of whole body insulin-mediated glucose disposal.

Plasma analyses. Plasma glucose, lactate, total cholesterol, HDL and LDL cholesterol, triglycerides, ALT, AST, and CRP were measured with reagents from Beckman, and free fatty acids (total) and ketones (total and 3-hydroxybutyrate) from Wako (Richmond, VA). Glycerol was measured using reagents from TG-B by Roche Diagnostics (Indianapolis, IN). Pyruvate was measured on a SpectraMax M2e plate reader from Molecular Devices (Sunnyvale, CA), using reagents from Sigma-Aldrich (St. Louis, MO) and a modification of the method by Hansen [3]. ELISAs were performed using the M2e plate reader with kits for total IGF-1 and human growth hormone from Alpco (Salem, NH); C-peptide and GIP from Millipore (St. Charles, MO); and glucagon from Mercodia (Uppsala, Sweden).

Plasma acylcarnitines and amino acids: Proteins were first removed by precipitation with methanol. Aliquoted supernatant was dried, and then esterified with hot, acidic methanol (acylcarnitines) or n-butanol (amino acids). Acylcarnitines and amino acids were analyzed by tandem mass spectrometry (MS/MS) using a Quattro Micro instrument (Waters Corporation, Milford, MA).

Amino acids and acylcarnitines were analyzed by flow injection electrospray ionization tandem mass spectrometry and quantified by isotope or pseudo-isotope dilution [4-10]. Briefly, plasma samples were spiked with a cocktail of heavy-isotope internal standards (Cambridge Isotope Laboratories, MA, USA; C-D-N, Isotopes, Canada) and deproteinated with methanol. Methanol supernatants were dried and esterified with either acidified methanol or butanol for acylcarnitine or amino acid analysis, respectively. Spectra were acquired using a Waters Acquity^{TM} UPLC system equipped with a TQ (triple quadrupole) detector and a data system controlled by MassLynx 4.1 operating system (Waters, Milford, MA).

Muscle and urine analyses. For muscle creatine and ATP, metabolites were extracted from 10mg of tissue in 0.5 M HClO4 (1 mM EDTA), then neutralized with 2.2 M KHCO3. ATP, creatine and phosphocreatine (PCr) content was determined using enzymatic spectrophotometric assays [11]. Briefly, for ATP and PCr, 25 µl of muscle extract was added to buffer containing 100 mM triethanolamine (pH 7.4), 10 mM magnesium acetate, 1 mM EDTA, 1 mM DTT, 1 mM NADP, 40 µM ADP, 5 mM glucose, and yeast G6PDH. Hexokinase and creatine kinase were then added sequentially, and change in absorbance was monitored for both reactions at 340nM. For creatine, 25 µl of muscle extract was added to buffer containing 100 mM glycine, 5 mM magnesium acetate, 30 mM KCl, 1.5 mM ATP, 1 mM PEP, 150µM NADH, LDH and pyruvate kinase. Creatine kinase was added, and change in absorbance was monitored at 340nM. Total creatine was calculated as the sum of creatine and PCr.

Muscle acyl CoA esters were analyzed using a method based on a previously published report by Magnes *et al*. [12] which relies on the extraction procedure described by Deutsch *et al*. [13]. The CoAs were further purified by solid phase extraction [14]. The acyl CoAs were analyzed by flow injection analysis using positive ion electrospray ionization on Quattro Micro, triple quadrupole mass spectrometer (Waters, Milford, MA).

Organic acids were analyzed by capillary gas chromatography/ mass spectrometry (GCMS) using isotope dilution techniques employing Trace Ultra GC coupled to a Trace DSQ MS operating under Excalibur 1.4 (Thermo Fisher Scientific, Austin, TX) [10]. Briefly, the supernatants of tissue homogenates were spiked with a mixture of heavy isotope labeled internal standards and the keto acids were stabilized by ethoximation. The organic acids were acidified and extracted into ethyl acetate. The extracts were dried and derivatized with N.O-bis(trimethylsilyl) trifluoroacetamide.

For non-targeted metabolomics, urine sample volume for preparation was normalized to creatinine levels, which were not different between groups (data not shown). Metabolites in a volume of urine equivalent to 2 micromoles of creatinine were then methoximated, extracted twice into ethyl acetate, dried, and trimethylsilylated. [15-18]. Molecules in prepped samples were then separated by capillary gas chromatography (GC), electron ionized (EI) at 70 eV, and filtered according to mass/charge ratio (*m/z*) using a single-quadrupole (quad) mass spectrometer (MS) scanning broadly from 600 to 50 m/z (6890N GC-5975 MS, Agilent Technologies, Santa Clara, CA). Peaks were deconvoluted using the Automated Mass spectral Deconvolution and Identification System (AMDIS) [19, 20]. Annotation of AMDIS-deconvoluted data features as metabolites was based on orthogonal comparison of both their observed GC retention times and their EI-mass-fragmentation patterns to several public and private spectral libraries, including Agilent's Fiehn GC/MS Metabolomics Retention-Time-Locked (RTL) library [15]. By making additions to the Fiehn library, our group has nearly doubled its size. This RTL spectral library now contains 2425 spectra from ~1400 compounds, making it one of the largest such RTL libraries for GC/EI-quad-MS metabolomics. Peak alignment and chemometrics of log-base-two-transformed areas of deconvoluted peaks were performed with our own custom macros written in Visual Basic for use in the Excel software environment (both from Microsoft, Redmond, WA). We then performed line-by-line manual curation to fix miscalls and to highlight ambiguities inherent in certain isomeric or otherwise similar metabolites.

Calculations. Leucine carbon flux is calculated as:

$$\text{Leucine } R_a = i \left(\frac{E_i}{E_{KIC}} - 1 \right)$$

where i is the tracer infusion rate (μmol • kg^{-1} • min^{-1}), E_i is the tracer purity (99%) and E_{KIC} is the tracer-to-tracee ratio (TTR) of α-KIC at steady state. Oxidation is calculated as:

$$\text{Leucine } R_{ox} = \frac{E_{CO_2}}{E_{KIC}} \left(\frac{V_{CO_2}}{k}\right)$$

where V_{CO_2} is total CO_2 production as measured by indirect calorimetry, E_{CO2} is the enrichment of $^{13}CO_2$ in the breath, and E_A is the plasma tracer enrichment. A standard bicarbonate correction factor (*k*) of 0.81 was used to account for retention of $^{13}CO_2$ [21, 22]. The non-oxidative portion of leucine flux (non-oxidative leucine disposal (NOLD); indicative of protein synthesis) is calculated as (whole body R_a – oxidation).

Indirect calorimetry (TrueMax 2400, ParvoMedics; Sandy, UT) was performed for 30 minutes prior to muscle biopsies. Muscle biopsies were obtained from the *vastus lateralis* using a 5 mm Bergström biopsy needle under sterile procedure and local anesthesia (2% lidocaine HCl). In muscle, the intracellular free TTR of phenylalanine were determined by GC-MS using L-[^{15}N] phenylalanine as an internal standard as described for plasma [23], and protein-bound phenylalanine TTRs were measured by GC-MS using an external standard curve approach [24] and selected ion monitoring of 239/237 (m+5/m+3) [25]. The fractional synthetic rate (FSR) of mixed muscle proteins was calculated from phenylalanine using the following equation:

$$\text{FSR} = \frac{(\Delta E_P \div t)}{[(E_{M1} + E_{M2}) \div 2]} \times 60 \times 100$$

where ΔE_p is the increment in protein-bound phenylalanine enrichment between the two biopsies, *t* is the time between biopsies and E_{M1} and E_{M2} are the phenylalanine enrichments in the free intracellular pool in the two biopsies. Data are expressed as percent per hour.

Exercise training. Participants were prescribed an aerobic training program based on their initial CPET results, estimated to expend ~5024 kJ (1200 kcal) per week at 65-80% of their VO_2 max via brisk treadmill walking with varying grade. Subjects were allowed to substitute an elliptical machine or stationary bike in cases of joint discomfort. Aerobic exercise was completed

during 3-4 sessions per week. Resistance training was performed 3 times per week, following aerobic exercise if performed on the same day. Following a ramping period (1 set for 2 weeks, 2 sets for 2 weeks), subjects performed 3 sets of 8-12 repetitions on the following machines: leg press, leg extension, seated leg curl, back extension, chest press, lat pulldown, seated row and shoulder press. Once a subject completed 3 sets of 12 repetitions in 2 consecutive sessions on a particular exercise, weight was increased by the next machine increment (usually 5 pounds). The CPET was repeated at the end of training to assess changes in aerobic fitness. The CPET was separated from any other post-training tests (OGTT, clamp, protein turnover) by a minimum of 3 days. Subjects continued their regular exercise program during the ~3-5 weeks it took to complete all post-tests.

In our previous exercise trials, mostly STRRIDE (Studies of Targeted Risk Reduction Interventions Through Defined Exercise), we have chosen six months as the standard period for the exercise intervention. This is a generally accepted standard in the field, based upon several considerations. First, this is generally believed to be a long enough exposure to have obtained the maximum but stable benefit and adaptation to the exercise stimulus. Second, the design of this study was based upon findings in STRRIDE-AT/RT in which the exercise exposure to a combined program was six months. In order to be able to generalize our findings here to those results, and vice versa, we believed it prudent to maintain six months as the study period. Third, it is generally held in the behavioral community that a habit that has been in place for at least six months is more likely to be maintained than if the behavior is in place for less than this period. Thus, this provides our work more implications for clinical applicability than it would if the period of exposure were less than six months.

Statistics. Study data were collected and managed using REDCap electronic data capture tools hosted at Duke University [26]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The Shapiro-Wilk test was used to assess the normality of each variable. If a variable was not normally distributed, simple transformations (i.e., log value or log (value+1)) were performed. If normality was not achieved by simple transformations, non-parametric tests were used as applicable. Percent change was calculated as ([OW-Trained value – OW-Untrained value]/OW-Untrained value)•100. Delta values are calculated as (OW-Trained) – (OW-Untrained) from a basal plasma or muscle (1^{st} biopsy) sample. In the OW group, post-intervention analyses were performed on the intent-to-treat (ITT) population, despite low compliance in 1 male (73%) and 1 female (53%) participant. When possible, all OW-Untrained subjects (n = 13) were included in comparisons against Controls. Removal of the 4 OW drop-out participants does not significantly alter results or interpretation.

Only baseline values were used to generate PCA factors. Metabolites with more than 25% of values below the lower limits of quantification were not analyzed (15/45 acylcarnitine species in plasma, 43/66 acylcarnitine species in muscle). Varimax rotation was used to produce identifiable factors. Factors with an eigenvalue ≥ 1.0 were retained based on the common Kaiser criterion. Metabolites with a factor load of ≥ 0.4 are reported as composing a given factor. Scoring coefficients were constructed and used to calculate factor scores for all subjects (weighted sum of the standardized metabolites within that factor, weighted on the factor loading

for each metabolite). Due to the small sample size, PCA was performed separately for plasma AA, AC and CM, and muscle AA, AC, OA, ceramides and CoAs.

REFERENCES:

[1] Duscha BD, Slentz CA, Johnson JL, et al. (2005) Effects of exercise training amount and intensity on peak oxygen consumption in middle-age men and women at risk for cardiovascular disease. Chest 128: 2788-2793
[2] DeFronzo RA (1992) Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. Diabetologia 35: 389-397
[3] Hansen JL, Freier EF (1978) Direct assays of lactate, pyruvate, beta-hydroxybutyrate, and acetoacetate with a centrifugal analyzer. Clin Chem 24: 475-479
[4] Wu JY, Kao HJ, Li SC, et al. (2004) ENU mutagenesis identifies mice with mitochondrial branched-chain aminotransferase deficiency resembling human maple syrup urine disease. The Journal of clinical investigation 113: 434-440
[5] An J, Muoio DM, Shiota M, et al. (2004) Hepatic expression of malonyl-CoA decarboxylase reverses muscle, liver and whole-animal insulin resistance. Nature Medicine 10: 268-274
[6] Millington DS, Stevens RD (2011) Acylcarnitines: analysis in plasma and whole blood using tandem mass spectrometry. Methods in molecular biology (Clifton, NJ) 708: 55-72
[7] Millington DS, Chace DH (1992) Carnitine and acylcarnitines in metabolic disease diagnosis and management. In: Desiderio DM (ed) Mass Spectrometry: Clinical and Biomedical Applications. Plenum Press, New York, pp 199 - 219
[8] Chace DH, Millington DS, Terada N, Kahler SG, Roe CR, Hofman LF (1993) Rapid diagnosis of phenylketonuria by quantitative analysis for phenylalanine and tyrosine in neonatal blood spots by tandem mass spectrometry. Clin Chem 39: 66-71
[9] Chace DH, Hillman SL, Millington DS, Kahler SG, Roe CR, Naylor EW (1995) Rapid diagnosis of maple syrup urine disease in blood spots from newborns by tandem mass spectrometry. Clin Chem 41: 62-68
[10] Jensen MV, Joseph JW, Ilkayeva O, et al. (2006) Compensatory responses to pyruvate carboxylase suppression in islet beta-cells - Preservation of glucose-stimulated insulin secretion. Journal of Biological Chemistry 281: 22342-22351
[11] Harris RC, Hultman E, Nordesjo LO (1974) Glycogen, glycolytic intermediates and high-energy phosphates determined in biopsy samples of musculus quadriceps femoris of man at rest. Methods and variance of values. Scand J Clin Lab Invest 33: 109-120
[12] Magnes C, Sinner FM, Regittnig W, Pieber TR (2005) LC/MS/MS method for quantitative determination of long-chain fatty acyl-CoAs. Analytical chemistry 77: 2889-2894
[13] Deutsch J, Grange E, Rapoport SI, Purdon AD (1994) Isolation and Quantitation of Long-Chain Acyl-Coenzyme A Esters in Brain Tissue by Solid-Phase Extraction. Analytical Biochemistry 220: 321-323
[14] Minkler PE, Kerner J, Ingalls ST, Hoppel CL (2008) Novel isolation procedure for short-, medium-, and long-chain acyl-coenzyme A esters from tissue. Anal Biochem 376: 275-276
[15] Kind T, Wohlgemuth G, Lee do Y, et al. (2009) FiehnLib: mass spectral and retention index libraries for metabolomics based on quadrupole and time-of-flight gas chromatography/mass spectrometry. Analytical chemistry 81: 10038-10048
[16] McNulty NP, Yatsunenko T, Hsiao A, et al. (2011) The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Sci Transl Med 3: 106ra106
[17] Roessner U, Wagner C, Kopka J, Trethewey RN, Willmitzer L (2000) Technical advance: simultaneous analysis of metabolites in potato tuber by gas chromatography-mass spectrometry. The Plant journal : for cell and molecular biology 23: 131-142
[18] Kouremenos KA, Pitt J, Marriott PJ (2010) Metabolic profiling of infant urine using comprehensive two-dimensional gas chromatography: Application to the diagnosis of organic acidurias and biomarker discovery. Journal of chromatography A 1217: 104-111

[19] Stein SE (1999) An integrated method for spectrum extraction and compound identification from gas chromatography/mass spectrometry data. Journal of the American Society for Mass Spectrometry 10: 770-781
[20] Halket JM, Przyborowska A, Stein SE, Mallard WG, Down S, Chalmers RA (1999) Deconvolution gas chromatography/mass spectrometry of urinary organic acids--potential for pattern recognition and automated identification of metabolic disorders. Rapid communications in mass spectrometry : RCM 13: 279-284
[21] Henderson GC, Fattor JA, Horning MA, Faghihnia N, Luke-Zeitoun M, Brooks GA (2007) Retention of intravenously infused [13C]bicarbonate is transiently increased during recovery from hard exercise. J Appl Physiol (1985) 103: 1604-1612
[22] Issekutz B, Jr., Paul P, Miller HI, Bortz WM (1968) Oxidation of plasma FFA in lean and obese humans. Metabolism 17: 62-73
[23] Patterson BW, Carraro F, Wolfe RR (1993) Measurement of 15N enrichment in multiple amino acids and urea in a single analysis by gas chromatography/mass spectrometry. Biological Mass Spectrometry 22: 518-523
[24] Calder AG, Anderson SE, Grant I, McNurlan MA, Garlick PJ (1992) THE DETERMINATION OF LOW D(5)-PHENYLALANINE ENRICHMENT (0.002-0.09 ATOM PERCENT EXCESS), AFTER CONVERSION TO PHENYLETHYLAMINE, IN RELATION TO PROTEIN-TURNOVER STUDIES BY GAS-CHROMATOGRAPHY ELECTRON IONIZATION MASS-SPECTROMETRY. Rapid Communications in Mass Spectrometry 6: 421-424
[25] Wolfe RR, Chinkes DL (2005) Isotope Tracers in Metabolic Research Principles and Practice of Kinetic Analysis. Wiley-Liss, Hobokon, NJ
[26] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 42: 377-381