Article Title: Comparative Effects of Single-Mode vs. Duration-Matched Concurrent Exercise Training on Body Composition, Low-Grade Inflammation, and Glucose Regulation in Sedentary, Overweight Middle-Aged Men.

Running Head: Concurrent vs. Single-Mode Exercise Training

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Abstract

The effect of duration-matched concurrent exercise training (CET) (50% resistance [RET] and 50% endurance [EET] training) on physiological training outcomes in untrained, middle-aged men remains to be elucidated. Forty-seven men (48.1±6.8y; 30.4±4.1kg·m^2) were randomized into 12-wks EET (40-60min cycling), RET (10 exercises; 3-4 sets×8-10 repetitions), CET (50% serial completion of RET and EET) or control condition. Intervention-based changes in fitness and strength; abdominal visceral adipose tissue (VAT), total body fat (TB-FM) and fat-free (TB-FFM) mass; plasma cytokines (CRP, TNFα, IL-6); muscle protein content of p110α and GLUT4; mRNA expression of GLUT4, PGC1α/β, cytochrome C oxidase (COX), hexokinase II (HKII), citrate synthase (CS); oral glucose tolerance and estimated insulin sensitivity were determined. CET promoted commensurate improvements of aerobic capacity and muscular strength, and reduced VAT and TB-FM equivalently to EET and RET ($P<0.05$), yet only RET increased TB-FFM ($P<0.05$). Although TNFα and IL-6 were reduced after all training interventions ($P<0.05$), CRP remained unchanged ($P>0.05$). EET reduced area-under-the curve for glucose, insulin and c-peptide, whilst CET and RET respectively reduced insulin and c-peptide, and c-peptide only ($P<0.05$). Notwithstanding increased insulin sensitivity index after all training interventions ($P<0.05$), no change presented for GLUT4 or p110α total protein, nor chronic mRNA expression of the studied mitochondrial genes ($P>0.05$). In middle-aged men, 12-wks duration-matched CET promoted commensurate changes in fitness and strength, abdominal VAT, plasma cytokines and insulin sensitivity, and an equidistant glucose tolerance response to EET and RET; despite no change of measured muscle mechanisms associative to insulin action, glucose transport and mitochondrial function.

Keywords: combined exercise; visceral obesity; interleukin; oral glucose tolerance; GLUT4; PGC1α.

Introduction

Skeletal muscle mass declines at the rate of ~5% per decade after the age of 30, and is further accelerated in advancing age and with declining physical activity levels (Drummond, Dreyer et al. 2008). Accompanying this atrophy, are concomitant reductions in mitochondrial and metabolic functioning, and increases of whole-body adipose, which in men, typically accumulate as visceral adipose tissue (VAT) in the abdominal region. Importantly, these age- and inactivity-related changes preclude subclinical abnormalities such as insulin resistance and atherosclerosis, and their clinical sequelae in type II diabetes (T2D) and cardiovascular disease (CVD) (Benton, Wright et al. 2008; Evans 2010; Parr, Coffey et al. 2012). Currently, middle-aged populations are advised to engage in resistance exercise training (RET) to offset atrophic processes and promote gains in muscle mass; and endurance exercise training (EET) for the augmentation of mitochondrial oxidative capacity and associated metabolic functioning, and reduction of total-body adipose and abdominal VAT (Haskell, Lee et al. 2007; Donnelly, Blair et al. 2009; Ismail, Keating et al. 2011; Ross, Hudson et al. 2012).

The serial completion of RET and EET, known as concurrent exercise training (CET), is reported to offer the respective benefits of RET and EET; however, previous studies of CET have involved addition of the full respective RET and EET interventions (Glowacki, Martin et al. 2004; Sigal, Kenny et al. 2007; Sillanpää, Häkkinen et al. 2009; Slentz, Bateman et al. 2011; Libardi, De Souza et al. 2012; Willis, Slentz et al. 2012). Thus, the metabolic and cardiovascular training outcomes reported in these studies may have presented due to an exacerbated dose-response rather than the effects of CET *per se* (Ross, Hudson et al. 2012). Notably, a recent acute study on untrained middle-aged men showed that duration-matched CET (50% RET + 50% EET) stimulated equivalent respective increases of myofibrillar and mitochondrial muscle protein synthesis as isolated RE or EE (Donges, Burd et al. 2012). Given this finding, and that the completion of a full RET plus EET program may not be temporally nor physically appropriate for initially untrained or time-deficient middle-aged cohorts, it is important to determine whether duration-matched CET offers comparable metabolic and cardiovascular health outcomes as completion of isolate RET or EET .

Specifically, health outcomes that are derivable from exercise training and which reflect a reduction in risk for T2D and CVD, include: 1) enhanced body composition, as evidenced by reduced abdominal VAT and total-body fat mass (TB-FM), and increased fat-free mass (TB-FFM) (Donnelly, Smith et al. 2004; Alberti, Zimmet et al. 2005; Ismail, Keating et al. 2011); 2) reduced chronic systemic low-grade inflammation, as indicated by systemic reductions of C-reactive protein (CRP), and the pro-inflammatory cytokines tumor necrosis factor-α (TNFα) and interleukin-6 (IL-6), and increases of cytokine receptors such as TNF-R1, TNF-R2, IL-6R, and IL-1 receptor antagonist (IL-1ra) (Steensberg, Fischer et al. 2003; Balducci, Zanuso et al. 2010; Libardi, De Souza et al. 2012); 3) increased insulin sensitivity and glucose uptake, as facilitated via the principal skeletal muscle glucose transporter 4 (GLUT4) (Goodyear and Kahn 1998; Hawley and Lessard 2008); and 4) increased mitochondrial functioning and oxidative capacity as reflected by chronically up-regulated mRNA expression of the mitochondrial co-transcription factors peroxisome proliferator–activated receptor-γ coactivator-1α (PGC1α) and β (PGC1β), and key mitochondrial and metabolic genes including cytochrome C oxidase (COX), hexokinase II (HKII), and citrate synthase (CS) (Arany, Lebrasseur et al. 2007; Tarnopolsky, Rennie et al. 2007; Wright, Han et al. 2007).

Notwithstanding the abovementioned training-induced alleviators of T2D and CVD risk, the literature lacks information pertaining to the effects of training mode on the aforesaid outcomes in untrained, overweight middle-aged men. As evidence, a recent meta-analysis of the effects of training mode on VAT reported that only EET was effective in reducing VAT (Ismail, Keating et al. 2011). However, this conclusion was drawn despite a large section of data being derived from EET (57%) or female-based studies (F=17; M=5), with only one male-based study comparing an alternate mode of training (RET) (Ismail, Keating et al. 2011). Furthermore, the literature indicates that cytokine profile may be improved (decreased TNFα-IL-6-CRP, and increased receptor presence) via reduced abdominal VAT after EET, or reduced TNFα after RET (Griewe, Cheng et al. 2001; Nicklas and Brinkley 2009; Lavie, Church et al. 2011); though, CET remains relatively unexamined, with inconsistent findings further existing for EET and RET (Lakka, Lakka et al. 2005; Nicklas and Brinkley 2009; Febbraio, Rose-John et al. 2010; Lavie, Church et al. 2011). Further, a meta-analysis of T2D participants reported that

CET was as effective as EET or RET in improving glucose control (Snowling and Hopkins 2006); although, EET interventions were primarily included (60%), and only one study concomitantly compared an alternate mode of training (Snowling and Hopkins 2006). Irrespective, the effect that CET has on glucose tolerance, insulin sensitivity and associative muscle mechanisms (GLUT4, p110α, PGC1α/β, HKII, CYTC, and CS) remains to be elucidated in untrained, middle-aged men.

The purpose of the present study was to concomitantly compare the effects of duration-matched CET, to RET and EET, in addition to a non-exercising control condition, for changes in known risk factors that are prognostically indicative of T2D and CVD. Given the recent finding of an equivalent acute response of duration-matched CET to RET and EET, we hypothesized that CET would promote commensurate training outcomes for the abovementioned training outcomes as RET or EET.

Methods

Participants

Forty-seven middle-aged (40-65y) men volunteered for this study (baseline participant data is presented in Table 1). Participants were sedentary at study baseline, which was defined as no regular pattern of planned or incidental exercise or physical activity >1d· wk^{-1} in the preceding 12 months. A physician overviewed participants medical history and pre-intervention data for pre-existing or new diabetes (fasting plasma glucose 7.0 $mmol \cdot L^{-1}$; 2 h post-challenge plasma glucose >11.1 $mmol \cdot L^{-1}$), cardiovascular disease, renal or hepatic disorders, immunological irregularities, abnormal leukocyte sub-populations, rheumatoid or osteo-arthritis, periodontal disease, chronic obstructive pulmonary disease, and any other condition associated with systemic inflammatory responses. Participants confirmed as having these conditions, or those taking lipid-lowering, anti-hypertensive, anti-inflammatory, or other potentially confounding medications were not involved in this study. Participants were provided with written and verbal information pertaining to testing and training procedures, and provided written informed consent prior to becoming involved in this study, which was approved by the institutional ethics committee and conformed to standards for the use of human subjects in research as outlined in the fifth revision of the Declaration of Helsinki.

Study Overview

After pre-screening and recruitment, all study participants attended an information seminar where all procedures were explained and discussed, including the maintenance of pre-intervention dietary patterns and avoidance of additional physical activity. Participants then attended a familiarization session where all aspects of testing and training were explained, demonstrated and rehearsed. After familiarization, participants attended two testing sessions in which the first test session involved computed tomography (CT) of the abdominal AT compartments, collection of a muscle biopsy from *m.* vastus lateralis, and a 2h 75g oral glucose tolerance test (OGTT). One week later, participants underwent a supine dual-energy x-ray absorptiometry (DXA) scan, followed by body mass, height, and waist and hip girth measurements, and further completed graded exercise and strength testing. Participants were then randomized into endurance (EET; *n*=13), resistance (RET; *n*=13) or combined (CET; *n*=13) exercise training or a non-exercising control condition (CON; *n*=8). Participants in the exercise groups completed 12-wk, $3 \cdot d \cdot wk^{-1}$ fully supervised, periodized and progressive programs, while the CON group maintained diet and physical activity patterns. After the 12-wk study period, participants returned to the laboratories, and in a standardized manner repeated all testing procedures.

Restriction of Dietary and Physical Activity Alterations

During the pre-study information seminar, all control and exercise group participants were verbally (and in writing via provided study information booklets) informed of the importance of maintaining their recent previous dietary and physical activity patterns. Accordingly, all participants were required to maintain food and beverage type, macronutrient composition, cooking preparation, portion size, consumption time, etc. as closely as possible to pre-study patterns during the 12-wk study period. Regarding physical activity control, although completely sedentary at study baseline, control participants were required to not engage in any additional planned or incidental physical activity, nor reduce any incidental activity. Participants in the exercise interventions were also requested to maintain their recent previous incidental physical activity patterns and to not engage in any additional planned or incidental physical activities during the 12-wk study period.

Exercise Interventions

Endurance Exercise Training

EET participants completed a program consisting primarily of cycle ergometry (CE) (828E, Monark Exercise AB, Varburg, Sweden) with elliptical cross training (XT) included mid-session to enhance training variety and adherence. Training started at 40min·session (15minCE:10minXT:15minCE) for wks 1-4, and increased to 50min·session (20CE:10XT:20CE) and 60 min·session (20CE:20XT:20CE) for wks 5-8 and 9-12, respectively. EET participants exercised at 75% and 80% of age-predicted maximal heart rate (HR_{max}) (INBAR, OREN et al. 1994) for wks 1-4, and 5-12, respectively.

Resistance Exercise Training

RET participants completed a whole-body training program including chest and shoulder press, seated rows, lat pulldown, leg press, leg curls, lunges, machine squats, and deadlifts. Participants completed 3×10 of each exercise at 75% of predicted 1RM for wks 1-4 (as described previously; (Donges, Duffield et al. 2010); and 4×8 at 80% 1RM for wks 5-12. In the first session of wks 5 and 9, 1RM was assessed and training resistance was altered accordingly. Participants completed a 5min warm-up on a rowing ergometer (Model D, Concept II, Morrisville, VT, USA), and subsequently completed the prescribed exercises in an alternating manner from upper- to lower-body, and completed compound multi-joint exercises (machine squats, deadlifts) prior to isolation exercises (leg curl, shoulder press).

Combined Exercise Training

CET participants serially completed 50% of the RET and 50% of the EET sessions. CET participants performed the same exercises on the same equipment, at the same relative intensity, and in the same order as RET and EET participants. For wks 1-4, 1.5 ×10 of each RE were completed at 75% 1RM, and was followed by 20min of EET at 75% HR_{max} (7.5CE:5XT:7.5CE). The second half set (5 repetitions) was completed at the same absolute resistance as the first set (10 repetitions) as to avoid having participants lift at a greater percent of RM for the second set (made possible due to reduced repetitions). For wks 5-8 and 9-12, participants completed 2×8 of RE at 80% 1RM, with 25 and 30min of EE at 80% HR_{max} (10CE:5XT:10CE) being respectively completed post-RE. As per RET, 1RM was assessed in wks 5 and 9 and lift resistance was altered accordingly.

Pilot RPE and VO_2 Consumption Testing of Exercise Modes

Despite the matching of modes for session duration, it is well accepted that matching EET and RET for their respective "energy costs", as is typically verified via VO_2 measurement, may be tenuous (Gaesser and Brooks 1984). Given that participants were sedentary at baseline, we chose to match the training programs according to session duration and session rating of perceived exertion (s-RPE), recorded 10min post-exercise. Pilot VO_2 data (K4b^2, Cosmed, Rome, Italy) were collected from a "representative" mid-program (wk-6) session, and included: EET = 50min cycle ergometry at 75% HR_{max}; RET = 10 exercises, 4×8 at 75% 1RM; CET = 25min cycle ergometry at 75% HR_{max} + 10 exercises of 2×8 at 75% 1RM. Despite the matching of duration and s-RPE between modes, significant differences in VO_2 were evident between EET (VO_2 mean = 24.6 $ml \cdot kg^{-1} \cdot min^{-1}$; VO_2 AUC = 4917 $ml \cdot kg^{-1} \cdot min^{-1}$) and RET ($VO_2$ mean = 12.3 $ml \cdot kg^{-1} \cdot min^{-1}$; VO_2 AUC = 2457 $ml \cdot kg^{-1} \cdot min^{-1}$), with CET showing an equidistant VO_2 response between the EET and RET modes (VO_2 mean = 19.4 $ml \cdot kg^{-1} \cdot min^{-1}$; VO_2 AUC = 3874 $ml \cdot kg^{-1} \cdot min^{-1}$ $P<0.05$). Notwithstanding that the above exercise training methodology may represent appropriate training stimuli for initially untrained, overweight cohorts; subsequent training outcomes should be interpreted according to the abovementioned differences in the session-based VO_2 response.

Measures

Computed Tomography

Participants presented in lightweight clothing, voided the bladder, and were positioned as central as possible in the gantry regarding vertex-pubis symphysis alignment. An anterior-posterior scanogram (scout radiograph) of the lower abdomen and pelvis was conducted using a 64-slice multi-detector CT (Toshiba Aquilion, Toshiba Medical Systems, Tokyo, Japan). A volume acquisition compartment 77 mm in length was obtained (120 kv, 50 mA and 0.5 sec tube rotation) cephalically from the superior end-plate of L4 during suspended inspiration. After scanning, eleven 7.0 mm contiguous axial images were reconstructed in a maximal display field of view (500 mm) for volume calculation with an attenuation range of -180 to -30 Hounsfield units, and the total (TAT), VAT and subcutaneous (SAT) compartments were determined as described previously (Couillard, Bergeron et al. 1999).

Muscle Biopsy Collection

After CT scan procedures, participants underwent procedures for the collection of a muscle biopsy from *m.* vastus lateralis at a site ~ 15cm superior to the patella. After administration of a local anaesthetic (2% plain Lignocaine), a 5mm Bergstrom needle modified with suction was inserted into an incision site for collection of a specimen which upon excision was promptly blotted on filter paper, removed of visible fat or connective tissue, frozen in liquid nitrogen, and stored at -80°C for ensuing Western blot and real-time polymerase chain reaction (RT-PCR) analyses.

OGTT and Venous Collection

After biopsy procedures, participants promptly underwent a 2h OGTT. For 3 days prior, participants had avoided physical activity and consumed >200 $g \cdot day^{-1}$ carbohydrate to help promote saturation of hepatic/muscular glycogen stores (Matsuda and DeFronzo 1999). During the 3 day period, diet was documented, and was checked for conformity by the research team, and replicated prior to the post-intervention OGTT. In the 24h prior to each OGTT, participants abstained from alcohol, and for 10h prior, had remained fasted, consuming only small amounts of water. After arrival, a catheter was inserted into an antecubital vein and a baseline blood sample (~20 mL) was drawn. Participants then ingested a 75g glucose beverage (Lomb Scientific, Thermo Fischer Scientific, NSW) in <5 min. Further blood samples (~10 mL) were drawn at 30min intervals post-ingestion. The trapezoidal rule was applied in calculating AUC for glucose, insulin and c-peptide (Le Floch, Escuyer et al. 1990).

Dual-Energy X-ray Absorptiometry and Anthropometry

Participants presented for test session two in a fasted (10h overnight) state in lightweight clothing free of metal-based accessories, and underwent dual-energy x-ray absorptiometry (DXA) to begin procedures. Participants were positioned centrally on the table of the DXA machine (Norland XR800, Cooper Surgical Company, Turnbull, CT, USA) and a supine total-body scan was carried out in which scanning resolution and speed were set at 6.5×13.0 mm and 260 $mm \cdot sec^{-1}$, respectively. Analysis of the scan (Illuminatus DXA, version 4.2.0, Turnbull, CT, USA) resulted in FM and FFM, reported both in absolute (0.1 kg) and relative (0.1 %) terms. Following scanning procedures, nude body mass, height, and waist and hip girth measurements were further obtained for each participant.

Exercise Testing

After DXA procedures, participants then completed a submaximal graded exercise test (GXT) on an electronically-braked cycle ergometer (LODE Excalibur Sport, LODE BV, Groningen, The Netherlands). The GXT commenced at 25W, and increased by 25W·min^{-1} until telemetry-based heart rate (Vantage NV, Polar, Finland) reached 80% of HR_{max} (Donges, Duffield et al. 2010). During the GXT, pulmonary gas exchange was measured by determining O_2 and CO_2 concentrations and ventilation to calculate VO_2 consumption using a calibrated metabolic gas analysis system (TrueOne 2400 metabolic system; Parvomedics; Sandy, Utah, USA). After ~30 min passive rest, and a 5 min light intensity warm-up on a rowing ergometer (Model D, Concept II, Morrisville, VT, USA) participants underwent 5 repetition-maximum (5RM) strength testing of the lower- and upper-body on a 45° leg press and seated chest press machine, respectively (Pannatta Sport, Apiro, Italy). Participants completed a set with light resistance to ensure machine adjustment (documented and standardized for post-testing). 5RM testing normally required 2 to 3 attempts (2 to 3 sets) with each attempt separated by ~3 min rest. 5RM strength testing procedures were utilized to identify strength whilst also minimizing soreness (due to participant's sedentary condition). As described previously, measured 5RM enabled approximation of the initial training resistance (Donges, Duffield et al. 2010).

Blood Analysis

Collected venous blood samples were aliquoted into fluoride oxalate tubes for analysis of glucose; lithium heparin tubes for analysis of insulin and c-peptide; EDTA tubes for cytokines; and SST for analysis of CRP, total cholesterol, high- and low-density lipoprotein cholesterol, and triglycerides. Samples were centrifuged at 3,500 rpm for 15 min at 4°C and stored at -80°C. All analytes were analysed according to the manufacturer instructions of the respective kits (Dade Behring Dimension Xpand, Siemens Diagnostics; Bio-Rad Variant HPLC, Sydney, Australia) as previously described in detail elsewhere (Donges, Duffield et al. 2010). Intra- and inter-assay co-efficient of variation (CV) were less than 5.2% for all measured analytes. Cytokines were analyzed in duplicate according to manufacturer's instructions with commercially available enzyme-linked immunosorbent kits (Quantikine®, R&D Systems, Minneapolis, MN). Intra- and inter-assay CV (highest CV is reported)

for the kits were: <4.6 % for TNFα (DTA00C); <3.7 % for TNF-R1 (DRT100); <3.5 % for TNF-R2 (DRT200); <8.0 % for IL-1ra (DRA00B); <3.3 % for IL-6 (D6050); <4.2 % for IL-6R (DR600).

Western Blot and RT-PCR Analysis

For Western blot procedures, powdered muscle was homogenized in ice-cold lysis buffer and extracted proteins were quantified using a BCA protein assay kit (Pierce, Auckland, New Zealand) (full procedural description is provided elsewhere (Donges, Burd et al. 2012). 50 μg of protein was then boiled and vortexed at 99°C for 7 min, loaded, separated by SDS-PAGE, and transferred to polyvinylidene difluoride membranes. After subsequent blocking procedures, membranes were incubated overnight at 4°C on a rocker with polyclonal antibodies (1:1000; Cell Signaling Technologies [CST], Auckland, New Zealand) specific for GLUT4 and p110α total protein and α-tubulin as a loading control. Detection with secondary antibodies (1:2000; horseradish peroxidase-conjugated goat anti-rabbit; Dako, Carpinteria, CA, USA) and enhanced chemiluminescence (ECL-Plus; Amersham Biosciences, Auckland, New Zealand) was made using a phosphorimager (FLA 4000, Fujifilm, Valhalla, NY, USA), and quantified by densitometry (Multi-gauge v3.0, Fujifilm, Valhalla, NY, USA). Pre- and post-intervention samples related to each person were run in adjacent lanes on the same gel.

For RT-PCR procedures (full procedural description is provided elsewhere; (Donges, Burd et al. 2012), powdered muscle was homogenized, and RNA isolated with TRIzol®Plus reagent (Invitrogen, Carlsbad, CA, USA) and chloroform, respectively. Isolated RNA was then mixed with glycogen in DEPC-tx H_2O and 1-Propanol in order to precipitate the RNA, which was tested for concentration and purity with a spectrophotometer (NanoDrop 1000 UV-Vis, NanoDrop® Technologies, New Zealand), and tested for size and density using an Agilent 2100 Expert Bioanalyser with the RNA 6000 Nano LabChip kit (Agilent technologies, Palo Alto, California, USA). Mean RNA integrity number (RIN) of RNA included in the study was 8.8±0.4; range of RIN: 7.4-9.2. RNA were then subsequently treated with DNase 1 (Invitrogen, Carlsbad, CA, USA), reverse-transcribed using a TaqMan® SuperScript™ VILO cDNA synthesis kit (Invitrogen, Carlsbad, CA, USA). TaqMan® Universal PCR Master Mix™ and TaqMan® Gene Expression assays (Perkin-

Elmer Applied Biosystems, Foster City, CA, USA) were then used to analyze mRNA of GLUT4 (Hs00168966_m1); PGC1α (Hs01016722_m1); PGC1β (Hs00991677_m1); COX (Hs02574374_s1); HKII (Hs00606086_m1); CS (Hs01588973_m1); and glyceraldehyde-3-phosphate dehydrogenase (Hs99999905_m1). All samples for each participant were simultaneously analyzed in triplicate in one assay run. PCR was performed using a7900HT Fast Real-Time PCR System and SDS 2.3 software (Perkin-Elmer Applied Biosystems, Foster City, CA, USA). Measurements of the relative distribution of each target gene were performed for each participant, then a cycle threshold (C_T) value was obtained by subtracting GAPDH C_T values from the respective target gene C_T values, and the expression of the target gene was then evaluated by the $^{\Delta\Delta}C_T$ algorithm (Pfaffl, Horgan et al. 2002).

Calculations

Insulin-sensitivity composite index (ISI_{comp}) was calculated according to the method of Matsuda and DeFronzo (Matsuda and DeFronzo 1999) as: $10000 / \sqrt{(Glu_0 \times Ins_0 \times Glu_{mean} \times Ins_{mean})}$, where Glu_{mean} and Ins_{mean} respectively represent mean plasma glucose and insulin concentrations during the OGTT (0-120 min inclusive).

Statistical Analysis

Data are presented as mean ± standard error of mean (SEM). One-way analysis of variance (ANOVA) tests were employed to examine baseline differences between groups. Subsequent to this, repeated measures two-way ANOVA (condition × time) tests were conducted to examine pre- to post-intervention changes within and between groups for aerobic capacity, muscular strength, body composition, plasma cytokines, muscle protein content, mRNA expression, glucose tolerance and insulin sensitivity. Tukey's HSD tests were applied post-hoc to determine the source of significance, which was set a priori $P \leq 0.05$. Data were checked and confirmed for normality of distribution via plotted analysis of change scores and baseline values (within-group), and Mauchley's sphericity tests (between group). Graphpad Prism© software and the trapezoidal rule were used to determine area under-the-curve (AUC) for the hormonal responses to the OGTT, with repeated measures ANOVA tests used to compare pre- and post-intervention differences within and between groups. All other statistical analyses were conducted with PASW Statistics (version 18.0 SPSS Inc, Chicago, IL).

Results

Intervention Compliance, and Aerobic Capacity and Muscular Strength Changes

All participants in the EET, RET, and CET groups attended and completed no fewer than 30 of the 36 supervised training sessions, with mean session attendance and completion rates of 33 of 36 sessions (92%±7%) for all three groups. Aerobic capacity and muscular strength data are presented in Table 2. At baseline there were no differences of aerobic capacity between groups ($P>0.05$); although the CON had greater lower-body strength than the RET group ($P<0.05$). There was no change of aerobic capacity or muscular strength after the CON intervention ($P>0.05$). In contrast, the EET intervention increased VO_2 ($L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$), time taken to reach 80% HR_{max}, and workload at 80% HR_{max}. The CET intervention also increased the abovementioned aerobic capacity measures ($P<0.05$), though no differences were evident following RET ($P>0.05$). Between-group comparisons revealed that EET increased VO_2 ($L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$) and workload at 80% HR_{max} more than the CON group ($P<0.05$); whereas CET increased these same measures greater than the CON and also the RET group ($P<0.05$). Following RET and CET, both upper- and lower-body strength were increased in each group ($P<0.05$); whilst only lower-body strength was increased after EET ($P<0.05$). Nevertheless, between-group analyses revealed that both the upper- and lower-body strength increases by the RET and CET groups were greater than that of both the EET and CON groups ($P<0.05$).

Total-Body Composition and Abdominal AT Compartmental Changes

Total-body (TB) composition and abdominal AT data are presented in Table 3. At study baseline, the EET group had greater body mass and absolute TB-FM compared to the CET group ($P<0.05$); yet, no other differences existed between groups ($P>0.05$). After the CON intervention, only a reduction of absolute TB-FFM was evident ($P<0.05$). In contrast, the EET intervention reduced body mass ($P<0.05$ vs. RET), with a reduction of absolute TB-FM ($P<0.05$ vs. CON), as well as a trend towards reduction of TB-FFM ($P=0.07$). In contrast, the RET intervention did not alter body mass ($P>0.05$); however, absolute TB-FFM increased ($P<0.05$ vs. EET), promoting an increase of relative TB-FM ($P<0.05$) despite no change of absolute TB-FM ($P>0.05$). The CET group concomitantly decreased and increased absolute TB-FM and TB-FFM ($P<0.05$), thus resulting in an increase of relative FM

(P<0.05 vs. CON). All three training interventions reduced abdominal VAT and SAT post-training (P<0.05), without differences between training groups or to the CON group (P>0.05).

CRP and Inflammatory Cytokine Changes

CRP and inflammatory cytokine data are presented in Table 4. At study baseline, differences were evident for basal concentrations of the studied cytokines (Table 4). Despite these baseline differences, no changes of CRP or inflammatory cytokine concentrations were observed after the CON period (P<0.05). Further, CRP, TNF-R1, IL-6R and IL-1ra concentrations remained unaltered in response to the training interventions (P>0.05). Conversely, all training interventions reduced IL-6 and TNFα concentrations (P<0.05), whilst EET promoted an increase of TNF-R2 concentration (P<0.05).

OGTT AUC Blood Chemistry Changes

Mode-specific AUC responses for glucose, insulin and c-peptide are presented in Figure 1. At study baseline, total AUC for insulin was greater in the EET group than the CON group (P<0.05). After the 12-wk period, there was no change of total AUC observed for the CON group (P>0.05). Conversely, the EET intervention resulted in reduced total AUC for glucose, insulin, and c-peptide post-training (P<0.05), while the CET intervention resulted in reduced total AUC for insulin and c-peptide (P<0.05). However, the RET intervention promoted reduced total AUC for c-peptide only (P<0.05).

Total Protein Content, mRNA Expression and Estimated Insulin Sensitivity

Representative blots for total protein of GLUT4, p110α and α-tubulin (A) and fold-change data for mRNA expression of GLUT4, PGC1α, PGC1β, COX, HKII, and CS (B) are presented in Figure 2; whilst estimated insulin functioning data are presented in Figure 3. There was no change of total protein content of GLUT4 or p110α, or chronic mRNA expression of any of the studied genes after training in any exercise mode (P>0.05). ISI_{comp} was significantly greater after all training modes (P<0.05), without differences between groups for these increases (P>0.05).

346 **Discussion**

347 In contrast to previous research that has investigated RET, EET and CET (Glowacki, Martin et al.
348 2004; Sigal, Kenny et al. 2007; Sillanpää, Häkkinen et al. 2009; Libardi, De Souza et al. 2012), the
349 current study employed a design in which CET participants serially completed 50% of a RET and an
350 EET session, rather than a full session of each mode (i.e. double the dose). Even so, in the current
351 study despite 50% less EET in each session, CET increased aerobic capacity to a similar extent as
352 EET (based on the heart rate and VO_2 responses to graded exercise testing). In addition, no
353 differences existed between CET and RET for gains in upper-body or lower-body muscular strength.
354 These findings of equivalent conditioning-based responses of CET are analogous to previous post-
355 training outcomes in isolated modes (Glowacki, Martin et al. 2004; Libardi, De Souza et al. 2012);
356 however, the current data demonstrates for the first time that concurrent completion of both a full
357 RET and a full EET session is not obligatory for equivalent induction of isolate-mode conditioning
358 responses in initially untrained, overweight middle-aged men.

359 The findings of this study also provide favourable evidence for the effects of duration-matched CET
360 on TB-FM; where unlike EET and RET, CET promoted equal reduction of absolute and relative FM.
361 However, an important distinction between CET and RET, is that RET promoted changes of FFM that
362 were not observed in CET. Previously we have shown in untrained middle-aged men that duration-
363 matched CET promotes acute myofibrillar FSR to the same extent as RET (Donges, Burd et al. 2012).
364 Collectively, the acute FSR and above finding imply that the RET component of CET may preserve
365 increases of FFM during EET-induced reductions of FM (considering a trend for reduction of FFM
366 after EET). Furthermore, despite not reducing absolute TB-FM to the extent of CET (-6.1%) or EET
367 (-4.5%), RET (-2.8%) promoted equivalent reduction of abdominal VAT. Accordingly, these results
368 provide information for the first time that the extent of FM reduction (in a 12-wk, 3d/wk program)
369 may not accurately reflect underlying effects on abdominal VAT. Thus, our data corroborate with a
370 recent meta-analysis (Ismail, Keating et al. 2011) in that whilst a dose-response relationship between
371 energy expenditure and weight loss appears reasonable, corresponding effects on TB-FM and VAT
372 may not be associated. This finding is supported by other randomized controlled trials that have also

reported VAT reduction without corresponding weight loss (Slentz, Aiken et al. 2005; Johnson, Sachinwalla et al. 2009). Additional research is needed to elucidate responsible mechanisms for the VAT reduction after RET; although, evidence indicates that intensity-derived lipolytic hormones such as growth hormone and hormone sensitive lipase may play a role (Beauregard, Utz et al. 2008).

Previous investigations have reported abdominal VAT to be an important contributor to circulating plasma concentrations of IL-6 and TNFα (Mohamed-Ali, Goodrick et al. 1997; Fried, Bunkin et al. 1998; Berg and Scherer 2005). Given that IL-6 and TNFα can stimulate and induce hepatic synthesis of CRP; a reduction of these markers would liken a reduction of basal CRP concentration (Yudkin, Stehouwer et al. 1999; Berg and Scherer 2005), and thus reduce prospective T2D (Pradhan, Manson et al. 2001) and CVD (Ridker, Hennekens et al. 2000) risk. Despite reduced abdominal VAT, and plasma IL-6 and TNFα concentration after all modes, no corresponding effects on CRP concentration were evident. Previously, Lakka et al. (Lakka, Lakka et al. 2005) reported no effect of EET on CRP concentration in participants with low (<1.0 $mg \cdot L^{-1}$) or moderate (1.0-3.0 $mg \cdot L^{-1}$) baseline concentrations; yet, a reduction was reported in participants with high concentrations (>3.0 $mg \cdot L^{-1}$). Moreover, we have previously observed a reduction of CRP (3.6 $mg \cdot L^{-1}$ to 2.4 $mg \cdot L^{-1}$) after 10-wk RET, and a trend (P=0.06) for EET to do the same (3.6 $mg \cdot L^{-1}$ to 3.0 $mg \cdot L^{-1}$) (Donges, Duffield et al. 2010). As the participants in our previous and current studies were similar with respect to age, body composition and physical conditioning, the lower baseline concentration of 1.6-2.3 $mg \cdot L^{-1}$ of participants in this study provides additional credence for the notion postulated by Lakka et al. (Lakka, Lakka et al. 2005) of a "regression towards a mean" effect (25); whereby CRP concentrations further elevated from the mean may be reduced to a greater extent. As such, despite reductions of systemic drivers of CRP synthesis and release (TNFα and IL-6), training did not reduce CRP concentration, owing to the prospect that concentrations were not elevated to a great enough extent (>3.0 $mg \cdot L^{-1}$) to warrant reduction within the studied 12-wk period.

Limited evidence exists for the effects of exercise training on concentrations of receptors capable of binding and inactivating pro-inflammatory cytokine activity (Febbraio, Rose-John et al. 2010).

Importantly, receptors such as TNF-R1 and TNF-R2, IL-6R, and IL-1ra, are suggested to offer respective anti-inflammatory properties via maintenance of reduced basal chronic TNFα, IL-6 and IL-1β concentrations (Ostrowski, Rohde et al. 1999; Febbraio, Rose-John et al. 2010). Our data revealed no effect of training on TNF-R1, IL-6R or IL-1ra concentrations; with only TNF-R2 being increased after EET. It has been postulated that increased presence of the TNF receptors permits greater binding and inhibitory activity of TNFα, thus endearing an anti-inflammatory effect within systemic circulatory tissues (Ostrowski, Rohde et al. 1999; Pai, Pischon et al. 2004). Given that TNFα was reduced more so after EET (-26%), than RET (-12%) or CET (-16%), it may be that an increased presence of TNF-R2 was influential in this response. Similarly, it has been postulated that increased systemic circulatory presence of IL-6R offers anti-inflammatory properties, where increased IL-6R presence is indicative of increased IL-6 binding, thus offering suppression of pro-inflammation as indicated via reduced basal IL-6 concentration (Keller, Penkowa et al. 2005; Febbraio, Rose-John et al. 2010). In this study, we observed IL-6 reductions after all training modes; yet there was no corresponding increase in IL-6R presence. Thus, our findings are not congruent with the aforesaid physiological affiliation and suggest a need for further research in elucidating the effects of exercise training on inflammatory cytokines and their associated receptors.

The effect that differing modes of training have on glucose tolerance in non-diabetic, overweight middle-aged men remains limited and inconsistent in the current literature. Of the previously mentioned studies investigating EET, RET or CET (Glowacki, Martin et al. 2004; Sigal, Kenny et al. 2007; Libardi, De Souza et al. 2012), none investigated glucose tolerance. The current study revealed that EET offered the greatest reduction in glucose, insulin and c-peptide AUC. Given the beneficial EET response, the lack of effect of RET on glucose and c-peptide AUC responses suggests that it was likely the EET, more so than the RET component of CET, that promoted the observed c-peptide and insulin AUC responses to CET. Other studies have reported decreased glucose and insulin AUC after EET or RET, and similar to the data here, with no between-group differences for AUC changes (Smutok, Reece et al. 1994; Rice, Janssen et al. 1999). Of these studies, one investigated EET and RET changes in combination with calorie restriction (Rice, Janssen et al. 1999), whilst the other

426 incorporated a notable difference in training frequency and session duration (EET = 5 $d \cdot wk^{-1}$ [60min]
427 vs. RET [30min] = 3 $d \cdot wk^{-1}$) (Smutok, Reece et al. 1994). Consequently, these methodological
428 discrepancies make it difficult to respectively determine the isolated effect of EET (Rice, Janssen et
429 al. 1999), or the dose-specific response (Smutok, Reece et al. 1994) from these studies. In a recent
430 study of EET, RET and CET on glucose tolerance in middle-aged men (Sillanpää, Häkkinen et al.
431 2009), CET participants completed both the full EET and RET programs; however, there was no
432 reduction of glucose or insulin AUC (Sillanpää, Häkkinen et al. 2009). As such, the data from the
433 current study provides novel information regarding duration-matched effects of all three training
434 modes on glucose, insulin and c-peptide AUC in middle-aged men; with EET promoting the greatest
435 reductions in AUC, while CET demonstrated a greater effect than RET alone.

436 Whilst not separating peripheral from central insulin resistance, ISI (comp) provides estimation of
437 whole-body insulin sensitivity in the context of both hepatic and peripheral tissues, considers insulin
438 sensitivity in the basal state, and is reported to correlate highly with corresponding euglycaemic-
439 insulin clamp results (Matsuda and DeFronzo 1999). In the current study, all modes significantly
440 increased ISI (comp), with no differences between modes for these increases. Improvements in insulin
441 action in skeletal muscle is mediated through facilitation of insulin signalling via the PI3K catalytic
442 sub-unit p110α, GLUT4-mediated trafficking of cytosolic glucose, and enhanced glucose utilization
443 and turnover in response to augmented mitochondrial function (Goodyear and Kahn 1998; Hawley
444 and Lessard 2008). However, a surprising finding here is the lack of change in these skeletal muscle
445 measures post-training. Whilst not measured here, the improvement in glucose tolerance (considering
446 no change in GLUT4 membrane/cytosolic content) may be partly attributed to an increase in glucose
447 effectiveness, which can account for up to 50% of glucose transport/uptake (Sakamoto, Higaki et al.
448 1999). We recently demonstrated that compared to EE, duration-matched CE was equally effective in
449 acutely increasing mitochondrial FSR, and acutely up-regulating and expressing PGC1α and PGC1β
450 mRNA (Donges, Burd et al. 2012). However in this study, phosphorylation and mRNA expression of
451 GLUT4 remained unaltered post-exercise; furthermore, HKII mRNA expression was acutely up-
452 regulated after EE (though not RE or CE), whilst COX and CS mRNA expression did not change

(Donges, Burd et al. 2012). Collectively, these acute and chronic findings from an analogous middle-aged cohort highlight similarities in GLUT4/COX/CS responses with no change of phosphorylation status/mRNA expression after a single bout (Donges, Burd et al. 2012); thus lending credence to the finding of no change in chronic levels of protein content/expression as reported here. Thus, in future studies of untrained middle-aged populations, it may be difficult, though more pertinent to measure GLUT4 translocation and associated PI3-kinase activity, rather than GLUT4 and p110α abundance.

In consideration of the above acute and chronic responses, why PGC1α/β/HKII expression was increased acutely in previous research of these modes (Donges, Burd et al. 2012), yet remained unchanged with respect to chronic expression here, remains unclear. Although speculative, it may be that single exercise bouts in untrained, overweight, middle-aged men, provide acute stimulation of mitochondrial FSR and PGC1α/β suggesting initiation of mitochondrial biogenesis (Donges, Burd et al. 2012). However, the chronic expression of PGC1α/β and further mitochondrial adaptation may be inhibited or down-regulated by other factors pertaining to age and genetic time-course i.e. increased calpain and caspase expression (Chen, Gong et al. 2000). Furthermore, age-related deleterious processes regarding mitochondrial dysfunction, such as up-regulated nuclear factor kappa β expression or reduced expression of longevity factors such as sirtuin 1 may also contribute to the lack of post-training mitochondrial marker expression (Lagouge, Argmann et al. 2006; Kramer and Goodyear 2007). Nonetheless, further corroboration of acute and chronic molecular muscle responses in middle-aged cohorts is warranted to elucidate the potential skeletal muscle molecular pathways responsible for the dose-specific adaptations to glucose regulation and insulin sensitivity noted earlier.

Whilst this study provides novel integrated adiposity, inflammation and glucose regulation data that are absent from the current literature, there are several limitations that should be considered when interpreting the study data. As reported earlier, it was not an exclusive purpose of this study to match the training modes for metabolic cost; although, our pilot VO_2 data did evidence differences between exercise modes, which may represent a bias in assumed energy expenditure and therefore related training outcomes (i.e. body composition, glucose tolerance, etc.). In addition, although VO_2

consumption was measured during a representative exercise bout, it may be ensuing post-exercise VO_2 responses that further assist explanation of the study data. Lastly, it should be acknowledged that although efforts were made by the research team to inform participants of the importance of maintaining their pre-study dietary habits at baseline and repeatedly throughout the interventions, and though diet was documented, overviewed by the research team, and replicated by participants prior to each test session, complete control of diet was not possible.

In conclusion, the data of this study show that duration-matched CET respectively increased measures of aerobic capacity and muscular strength equivalently to EET and RET. The body composition data indicate an equivalent effect of training on abdominal VAT; yet, the reduction of VAT in response to RET is a finding of note, as RET did not reduce absolute TB-FM. Moreover, where EET may show a tendency for FFM reduction in the wake of FM reduction, CET offers FFM preservation in addition to FM reduction. Nevertheless, despite VAT and TB-FM reduction, and reductions of TNFα and IL-6, there was no corresponding reduction of CRP concentration, nor concentrations of cytokine receptors (TNF-R1, IL-6R, IL-1ra). The OGTT data revealed that EET reduced AUC for glucose, insulin and c-peptide, where CET reduced insulin and c-peptide, and RET reduced c-peptide only. Lastly, all training modes increased estimated insulin-sensitivity, despite no change of total protein content of GLUT4 and p110α, nor mRNA expression of GLUT4, PGC1α/β, COX, HKII, or CS, thus emphasizing a need for further examination of other unstudied skeletal muscle mechanisms. In summary, for an identical time investment, duration-matched CET improved physical conditioning, abdominal VAT, relative TB-FM, plasma TNFα and IL-6, and ISI as either full RET or full EET; however, RET and EET respectively evidenced a greater capacity to increase FFM and reduce the OGTT hormonal response.

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690

Table 1. Baseline Subject Characteristic Data.

Measure	EET (1)	RET (2)	CET (3)	CON (4)
Age (*yr*)	45.4 ± 1.7	51.7 ± 2.1	46.2 ± 1.4	49.5 ± 2.6
Height (*cm*)	179.0 ± 1.4	180.3 ± 1.3	179.0 ± 1.7	176.5 ± 0.01
Body Mass (*kg*)	103.1 ± 4.6 ^2	96.4 ± 3.3	96.4 ± 1.7	92.2 ± 6.9
BMI ($kg^{-1} \cdot m^{2}$)	32.0 ± 1.3	29.7 ± 0.9	30.2 ± 0.7	29.6 ± 2.1
Waist girth (*cm*)	104.8 ± 3.1	103.3 ± 2.2	101.3 ± 1.9	100.9 ± 4.3
WHR	0.96 ± 0.02	0.98 ± 0.02	0.96 ± 0.02	0.97 ± 0.02
Total cholesterol ($mmol \cdot L^{-1}$)	5.27 ± 0.27	4.87 ± 0.18	5.76 ± 0.32 ^2	4.83 ± 0.45
LDL cholesterol ($mmol \cdot L^{-1}$)	3.08 ± 0.23	2.92 ± 0.17	3.58 ± 0.26 ^2	2.86 ± 0.38
HDL cholesterol ($mmol \cdot L^{-1}$)	1.30 ± 0.07	1.29 ± 0.07	1.39 ± 0.07	1.26 ± 0.14
Triglycerides ($mmol \cdot L^{-1}$)	2.00 ± 0.39	1.45 ± 0.19	1.69 ± 0.15	1.56 ± 0.31
Glucose ($mg \cdot dL^{-1}$)	5.62 ± 0.14	5.35 ± 0.13	5.53 ± 0.15	5.48 ± 0.19
Insulin ($\mu IU \cdot mL^{-1}$)	12.8 ± 2.3	11.5 ± 1.8	13.1 ± 2.9	10.4 ± 2.5
C-peptide ($ng \cdot mL^{-1}$)	2.83 ± 0.33	2.64 ± 0.22	2.45 ± 0.19	2.47 ± 0.44
HbA1c (*%*)	5.4 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.4 ± 0.1

Data are reported as mean ± standard error of the mean. EET ([1]), endurance exercise group, *n*=13; RET ([2]), resistance exercise group, *n*=13; CET ([3]), concurrent exercise group, *n*=13; CON ([4]), control group, *n*=8. BMI, body mass index; WHR, waist to hip ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycosylated haemoglobin. ^Significant difference to denoted (1-4) group at baseline ($P<0.05$).

Table 2. Aerobic Exercise Capacity and Muscular Strength Data.

Measure		EET (1)	RET (2)	CET (3)	CON (4)
VO_2 at 80% HR_{max}	Pre	2.30 ± 0.14	1.94 ± 0.11	2.01 ± 0.12	2.07 ± 0.20
($L \cdot min^{-1}$)	Post	2.89 ± 0.17 *	2.17 ± 0.15	2.70 ± 0.11 *	2.06 ± 0.19
	% Δ	+27 ± 6 †4	+13 ± 7	+37 ± 7 †2,4	+2 ± 7
VO_2 at 80% HR_{max}	Pre	22.5 ± 1.4	20.3 ± 1.1	21.0 ± 1.3	22.8 ± 2.1
($ml \cdot kg^{-1} \cdot min^{-1}$)	Post	28.6 ± 1.2 *	22.8 ± 1.6	28.3 ± 1.2 *	22.9 ± 2.5
	% Δ	+30 ± 6 †4	+13 ± 7	+38 ± 6 †2,4	+2 ± 8
Time to 80% HR_{max}	Pre	444 ± 20	374 ± 22	401 ± 28	354 ± 42
(*sec*)	Post	549 ± 35 *	392 ± 28	521 ± 29 *	314 ± 54
	% Δ	+23 ± 5 †4	+6 ± 6	+35 ± 9 †4	-5 ± 17
Workload at 80% HR_{max}	Pre	198 ± 9	169 ± 9	179 ± 11	159 ± 17
(*Watts*)	Post	240 ± 14 *	171 ± 12	227 ± 11 *	144 ± 24
	% Δ	+21 ± 4 †4	+2 ± 7	+30 ± 7 †2,4	-3 ± 17
Leg press	Pre	148 ± 13	130 ± 10	156 ± 11	190 ± 13 ^2
(*kg*)	Post	186 ± 16 *	258 ± 15 *	267 ± 19 *	183 ± 16
	% Δ	+28 ± 6	+99 ± 10 †1,4	+73 ± 9 †1,4	-4 ± 7
Chest press	Pre	66 ± 3	53 ± 4	67 ± 2	62 ± 5
(*kg*)	Post	73 ± 4	87 ± 4 *	92 ± 4 *	64 ± 7
	% Δ	+11 ± 5	+68 ± 11 †1,4	+38 ± 2 †1,4	+3 ± 4

Data are reported as mean ± standard error of the mean. EET (1), endurance exercise group, *n*=13; RET (2), resistance exercise group, *n*=13; CET (3), concurrent exercise group, *n*=13; CON (4), control group, *n*=8. % Δ = mean percent change from baseline (pre-intervention). ^Significant difference to denoted (1-4) group at baseline (P<0.05); *Significant within-group change from baseline (P<0.05); †Significant between-group change from baseline (P<0.05). HR_{max}, heart rate maximum.

Table 3 - Body Composition and Abdominal Adipose Tissue Data.

Measure		EET (1)	RET (2)	CET (3)	CON (4)
Body mass (*kg*)	Pre	103.1 ± 4.6 ^3	96.4 ± 3.3	96.4 ± 1.7	92.2 ± 6.9
	Post	101.1 ± 4.4 *	96.6 ± 3.4	95.7 ± 1.7	92.3 ± 7.2
	% Δ	-1.9 ± 0.7 †2	+0.2 ± 0.2	-0.7 ± 0.7	+0.1 ± 0.6
TB-FFM (*kg*)	Pre	72.1 ± 2.6	67.5 ± 1.8	71.0 ± 1.4	67.4 ± 3.7
	Post	71.5 ± 2.4	68.5 ± 1.9 *	71.7 ± 1.3	66.9 ± 3.7 *
	% Δ	-0.8 ± 0.7	+1.5 ± 0.6 †1	+1.1 ± 0.5	-0.8 ± 0.3
TB-FM (*kg*)	Pre	29.7 ± 2.5 ^3	27.5 ± 2.0	23.6 ± 1.4	23.2 ± 3.8
	Post	28.4 ± 2.4 *	26.8 ± 2.0	22.2 ± 1.5 *	23.9 ± 4.1
	% Δ	-4.5 ± 1.6 †4	-2.8 ± 1.1	-6.1 ± 2.4 †4	+2.4 ± 2.5
TB-FM (*%*)	Pre	27.8 ± 1.3	27.6 ± 1.4	24.0 ± 1.2	23.9 ± 2.2
	Post	27.0 ± 1.3 *	26.8 ± 1.3 *	22.6 ± 1.3 *	24.4 ± 2.3
	% Δ	-2.8 ± 1.2	-2.9 ± 1.0	-5.6 ± 1.9 †4	+2.2 ± 2.1
SAT (cm^2)	Pre	2382 ± 155	2177 ± 122	2144 ± 141	2039 ± 205
	Post	2263 ± 139 *	2102 ± 133 *	2048 ± 141 *	2071 ± 225
	% Δ	-4.4 ± 1.7	-4.0 ± 1.7	-4.4 ± 1.7	+1.8 ± 1.6
VAT (cm^2)	Pre	1371 ± 113	1451 ± 114	1251 ± 133	1383 ± 164
	Post	1222 ± 100 *	1269 ± 106 *	1100 ± 95 *	1349 ± 145
	% Δ	-10.3 ± 2.3	-12.2 ± 2.6	-8.6 ± 4.2	-0.7 ± 1.5

Data are reported as mean ± standard error of the mean. EET ([1]), endurance exercise group, *n*=13; RET ([2]), resistance exercise group, *n*=13; CET ([3]), concurrent exercise group, *n*=13; CON ([4]), control group, *n*=8. % Δ = mean percent change from baseline (pre-intervention). ^Significant difference to denoted [1-4] group at baseline (P<0.05); *Significant within-group change from baseline (P<0.05); †Significant between-group change from baseline (P<0.05). TB-FM, total body fat mass; TB-FFM, total body fat free mass; SAT, subcutaneous adipose tissue; VAT, abdominal visceral adipose tissue.

Table 4. Plasma CRP and Inflammatory Cytokine Data.

Measure		EET (1)	RET (2)	CET (3)	CON (4)
CRP ($mg \cdot L^{-1}$)	Pre	2.25 ± 0.37	2.21 ± 0.30	1.88 ± 0.27	1.60 ± 0.09
	Post	2.33 ± 0.21	2.38 ± 0.31	1.91 ± 0.34	1.89 ± 0.32
	% Δ	+3 ± 13	+8 ± 9	+1 ± 14	+18 ± 19
TNFα ($pg \cdot mL^{-1}$)	Pre	4.42 ± 0.33	7.14 ± 0.43 ^1	5.21 ± 0.66	6.11 ± 0.25 ^1
	Post	3.29 ± 0.29 *	6.23 ± 0.32 *	4.39 ± 0.41 *	6.19 ± 0.33
	% Δ	-26 ± 10	-12 ± 5	-16 ± 10	+1 ± 7
TNF-R1 ($pg \cdot mL^{-1}$)	Pre	166 ± 8	149 ± 8	140 ± 7	139 ± 12
	Post	168 ± 8	157 ± 9	133 ± 6	138 ± 11
	% Δ	+1 ± 2	+5 ± 3	-5 ± 3	-1 ± 2
TNF-R2 ($pg \cdot mL^{-1}$)	Pre	320 ± 13 ^3,4	315 ± 18 ^3,4	257 ± 13	247 (72)
	Post	330 ± 13 *	297 ± 15	262 ± 16	247 (86)
	% Δ	+3 ± 1	-6 ±6	+2 ± 4	+1 ± 3
IL-6 ($pg \cdot mL^{-1}$)	Pre	1.94 ± 0.31	2.74 ± 0.69	2.35 ± 0.31	1.93 ± 0.60
	Post	1.28 ± 0.26 *	1.84 ± 0.53 *	1.91 ± 0.26 *	1.88 ± 0.94
	% Δ	-34 ± 11	-33 ± 18	-19 ± 6	-3 ± 19
IL-6R ($pg \cdot mL^{-1}$)	Pre	693 ± 48	739 ± 50	743 ± 63	691 ± 71
	Post	719 ± 48	684 ± 48	674 ± 60	653 ± 83
	% Δ	+4 ± 4	-7 ± 4	-9 ± 1	-6 ± 2
IL-1ra ($pg \cdot mL^{-1}$)	Pre	572 ± 51	484 ± 48	692 ± 36 ^2,4	496 ± 87
	Post	557 ± 49	474 ± 44	676 ± 55	496 ± 77
	% Δ	-3 ± 7	-2 ± 12	-2 ± 8	+1 ± 15

Data are reported as mean ± standard error of the mean. EET ([1]), endurance exercise group, *n*=13; RET ([2]), resistance exercise group, *n*=13; CET ([3]), concurrent exercise group, *n*=13; CON ([4]), control group, *n*=8. % Δ = mean percent change from baseline (pre-intervention). ^Significant difference to denoted (1-4) group at baseline (P<0.05); *Significant within-group change from baseline (P<0.05); †Significant between-group change from baseline (P<0.05). CRP, C-reactive protein; TNFα, tumor necrosis factor α; TNF-R1, TNF receptor one; TNF-R2, TNF receptor two; IL-6, interleukin 6; IL-6R, IL-6 receptor; IL-1ra, IL-1 receptor antagonist.

Figure Legends

Figure 1.

Data are total concentration area under-the-curve (AUC) reported as mean ± standard error of mean for: (A) glucose; (B) insulin; (C) C-peptide, measured after EET ([1]), endurance exercise training, *n*=13; RET ([2]), resistance exercise training, *n*=13; CET ([3]), combined exercise training, n=13; CON ([4]), control condition, *n*=8. ^Pre-intervention difference to EET (P<0.05); *Different to pre-intervention (P<0.05).

Figure 2.

(A) Representative blots of total protein measured pre- and post-intervention following EET, endurance exercise training; RET, resistance exercise training; CET, combined exercise training; CON, non-exercising control group. GLUT4, glucose transporter 4; p110α, phosphoinositide-3-kinase catalytic subunit α. (B) Data are mean ± standard error of mean fold-changes of mRNA expression measured pre- and post-intervention following EET, endurance exercise training; RET, resistance exercise training; CET, combined exercise training; CON, non-exercising control group. GLUT4, glucose transporter 4; peroxisome proliferator–activated receptor-γ coactivator-1 α (PGC1α) and β (PGC1β); COX, cytochrome C oxidase; HKII, hexokinase II; and CS, citrate synthase.

Figure 3.

Data are relative changes (Δ) of estimated insulin sensitivity composite index ($_{est}$ISI (comp)) reported as mean ± standard error of mean, following EET ([1]), endurance exercise training, *n*=13; RET ([2]), resistance exercise training, *n*=13; CET ([3]), combined exercise training, n=13; CON ([4]), control condition, *n*=8. *Different to pre-intervention (P<0.05).