**Supplemental Content 1 – Supplemental Methods**

*Purcell et al. 2021; Diet versus Exercise in Obesity*

**Exclusion criteria**

Exclusionary criteria included history of diabetes mellitus or cardiovascular disease; uncontrolled hypertension (blood pressure >140/90 mm Hg), uncontrolled thyroid disease (thyroid stimulating hormone <0.5 or >5.0 IU/mL), or dyslipidemia; renal disease or hepatic disease; any cardiac, pulmonary, neurological, or orthopedic condition contraindicating exercise; current smoking; use of medications that may affect energy intake or energy expenditure in the past six months; >5% weight loss or gain in the previous six months; currently pregnant, lactating or < 6 months post-partum; previous bariatric surgery; major psychiatric disorder; presence of alcohol or substance abuse; current depression via medical history and/or score >21 on the Center for Epidemiologic Studies Depression Scale [1], or history of eating disorders and/or score of >20 on the Eating Attitudes Test [2].

**Exercise Intervention**

AEX participants were instructed to perform aerobic exercise on a motor-driven treadmill at the University of Colorado Anschutz Health and Wellness Center fitness facility a minimum of four times/week. Alternate aerobic activities (e.g., elliptical, stationary bike) were permitted for 20% of sessions. Because exercise prescriptions were based on heart rate, participants could complete their exercise via walking, jogging, or running. Participants were provided with a Technogym Wellness System Key (Technogym USA Corporation, Seattle, Washington), which interfaced with the Technogym cardiovascular equipment at the fitness facility. The first session was supervised by research staff and participants met with a research assistant weekly to enhance compliance to exercise frequency and intensity targets. Exercise compliance was attained from the TechnoGym System on a weekly basis. Adherence was defined as the total number of minutes exercised as recorded by the TechnoGym System over the 12 weeks divided by 2060 minutes (total prescribed) and expressed as a percentage. Individualized exercise prescriptions were developed using age-predicted maximum heart rate (220-age). Exercise sessions were preceded by a 2 to 5-minute warm-up performed at a heart rate corresponding to 50-60% predicted maximum. The duration of exercise sessions at baseline were 15 minutes at 60-65% predicted heart rate maximum and gradually increased in 5-minute increments to 45-minute sessions at 75-80% predicted heart rate maximum by weeks 11 and 12.

**Diet intervention**

Measured RMR x 1.3 was used as an approximate benchmark to estimate calorie goals, in line with previous successful weight loss interventions conducted at our center [3–5]. Participants attended weekly, instructional meetings with a registered dietitian or research assistant. Sessions varied between 15 – 60 minutes based on the topic and participant engagement. Curriculum were based on a standard and previously published behavioral weight loss program [6]; there were no stipulations regarding dietary composition, but the program generally supported a balanced distribution of macronutrients similar to the Acceptable Macronutrient Distribution Ranges [7]. Participants were taught basic dietary tracking practices to help meet their energy intake restriction goal, enhance awareness, and ensure continued commitment to the study. Participants used the MyFitnessPal application [8] to record daily dietary intake and shared these results with the study team for review and feedback each week. Because dietary intake analysis is resource-intensive and potentially inaccurate for energy intake assessment, there was no comparison between actual and goal energy intake for adherence in the DIET group. Instead, adherence was defined as the average number of days each participant tracked their dietary intake divided by seven (days/week).

**Energetic compensation to each intervention**

We defined compensation – or the difference between predicted and observed weight loss – in each intervention according to previously-established calculations [9, 10]. Specifically, compensation was defined as:

Where Δ FM and Δ FFM are expressed in kilograms and multiplied by their respective energy content (i.e., FM: 9500 kcal/kg, FFM: 1200 kcal/kg) and thermogenic adjustments were changes in RMR in kcal/day. Zero compensation is indicative of body energy stores that changed exactly as expected, 100% compensation is indicative of body energy stores that remained the same, and -100% compensation is indicative of body energy stores that decreased by twice as much as expected. Within the DIET group, total prescribed energy deficit was defined as 42,000 kcal (500 kcal deficit/week x 12 weeks). Within the EX group, total prescribed energy deficit was defined as estimated energy expenditure from exercise [10]:

Where VO2max was the maximal oxygen consumption attained from a graded exercise test on a motor-driven treadmill at baseline (in L/kg/min), body weight was in kilograms, total prescribed exercise duration was 2060 minutes, and 5 was the estimated energy expenditure per liter of oxygen consumption.

***Ad libitum* dietary intake**

After the 180-minute appetite evaluation and blood sampling, participants were offered a lunch meal at the CTRC consisting of 1800 kcal from lasagna, salad, two types of salad dressing (a vinaigrette and a ranch option), dinner rolls, butter, cheese, pound cake, strawberries, diet soda, and a regular soda. Participants were instructed to eat as much or as little as they wanted and had the option to request more of any item. Immediately after the study visit, participants were given a 3-day *ad libitum* diet that consisted of 80% of estimated total daily energy intake requirements plus a snack box containing 2600 kcal (55% carbohydrate, 35% fat, 10% protein) each day. Participants reported to the CTRC each morning and returned containers and any uneaten food from the previous day, which were then weighed and recorded with ProNutra Software (Viocare, Kingston, NJ, USA). Participants were instructed to eat as much or as little as they wanted and were asked to only eat the provided food.

**Non-exercise physical activity and sedentary behaviors**

ActivPAL data were downloaded using the manufacturer software (V8, PAL technologies, Glasgow, Scotland) and processed using the ProcessingPAL-V1.2 software (https://github.com/UOL-COLS/ProcessingPAL/releases). An automated algorithm [11] identified sleep/non-wear windows as the longest bout in a 24-hour period that lasted ≥ 2 hours or any very long bouts lasting ≥ 5 hours. Activity bouts within 15 minutes of the identified sleep window were categorized as either waking wear (if there was movement) or additional sleep/non-wear (if there was no/limited movement). Finally, the program identified invalid days based on limited variation in activities (≥95% of waking wear time in any single activity), <500 steps/day, or <10 hours of wear time. Data in the present analyses were used if ≥3 days of valid days were available. Heat maps of activity were visually inspected for plausibility of sleep/non-wear time by an investigator (S.A.P.) with additional inspection by others (S.A.C., J.M.B.) as needed and comparison to activity and sleep logs completed by participants to limit misidentification. In the case of clear error (i.e., sleep measured as awake time), the bouts were manually re-categorized using the ‘corrections’ function of ProcessingPAL. Non-exercise physical activity and sedentary behavior were estimated by removing exercise sessions, where applicable.

The activPAL software classified behaviors (sitting/lying, standing, stepping) and assigned metabolic equivalency of task (MET) values for behaviors events using a linear regression algorithm applied within the manufacturer’s software. METs for stepping events were assigned using a cadence-based algorithm, as previously validated in healthy adults [12, 13]. Sitting/lying events were assigned 1.20 METs and are considered ‘sedentary’ for the present analysis. Standing events were assigned 1.50 METs. Stepping events were categorized as light physical activity (LPA; 1.50-2.99 METs) or moderate-to-vigorous physical activity (MVPA; ≥3.00 METs), using 75 steps/minute as a threshold for MVPA. This analysis investigated average steps/day, the number of sedentary bouts/day, number of sedentary bouts >60 minutes/day and percent of waking time spent in sedentary, standing, LPA, and MVPA.

**References**

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