Supplementary Online Content

Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese, older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2015.17346.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Supplemental Details on Statistical Analyses

Determination of Effect Size and Sample Size

If the main effect of Diet or Exercise resulted in a 10% increase in peak VO_2, that would be considered statistically significant. Given that this is a factorial design, the main effect of one intervention is the average of the effects of that intervention with and without the presence of the other outcome. Allowing for the possibility of an interaction between the effects, the study was designed to allow for an interaction up to 10%, and 2% for an intervention depending on the presence or absence of the other intervention for an average main effect of 6%.

The sample size needed to achieve these aims is proportional to $Vx(1-r^2)$, where V is the variance and r is the correlation between the outcome measure and the baseline measure. Based on our preliminary and related studies with Exercise (E) and Diet (D) interventions with patients with BMI $\geq$ 30 who underwent exercise training, the mean, standard deviation (SD), and r for peak VO_2 were 1299, 385, and 0.957, respectively. The sample size needed to detect a 6% main effect with 80% power is 66 evaluable patients. For quality of life, using preliminary data from the same study, the total score mean, SD, and r were 25.6, 23.5, and 0.94, such that 79 evaluable patients are needed to detect a 20% main effect of either intervention with 80% power. Thus, 80 evaluable participants would provide $\geq$80% power to detect a main effect of 6% in peak VO_2, and effect size of 20% on MLHF total score, the co-primary outcomes. Allowing for up to 20% loss to follow-up, 100 subjects were randomized to the four groups.

Interaction

Because the test for interaction is a test of a linear contrast of the four individual randomized groups, it is well known to have low power. In order to minimize false negatives, tests for interactions were conducted at the 10% level of significance. If the p-value was $\geq$ 0.10, the effect of the two interventions were considered additive (or 'complementary') which is equivalent to saying the difference between the Least Square means of the Exercise+Diet group minus the control group is not statistically different than the sum of the Exercise main effect plus the Diet maim effect. If this difference is significantly greater than the sum of the two main effects then the two interventions would be considered super-additive (or 'synergistic'). If this contrast was statistically less than the sum of the two main effects then the two interventions would be considered to have a 'sub-additive effect'.

Multiple Comparisons

The trial was designed to have two co-primary outcomes, peak VO_2 (ml/kg/min) and the Minnesota Living with Heart Failure questionnaire (MLHF) total score.

The results section declares exploratory outcome variables to be significant if the unadjusted (for multiple comparisons) p-value is < 0.05. If one desired to perform a subsequent analysis to adjust for multiple comparisons, then one would use the Bonferonni technique to determine the critical p-value required to declare significance. The exploratory outcome measures are logically grouped in 4 domains: exercise function (12 individual measures), quality of life (2 individual measures), body composition (13 individual measures), and cardiac function (10 individual measures). Each domain is conceptually different and deserves to be tested at their own 5% two-sided level of significance. If adjusting for the multiple measures within each domain using Bonferroni's adjustment for multiple outcomes, results would show exercise performance to be significant if any of its measures have an unadjusted p-value < 0.004, quality of life if any of its measures have an unadjusted p-value < 0.025, body composition if any of its measures have an unadjusted p-value < 0.004, and left ventricular function if any of its measures have an unadjusted p-value < 0.005.

After adjustment for multiple comparisons, most of the significant effects reported in the results section remained significant with the exception of the diet effect on peak VO_2 (expressed as ml/kglean/min), peak VO_2 (expressed as ml/kgleglean/min), VO_2 reserve (ml/min), Leg muscle quality (w/cm^2), MRI measure of end diastolic volume (ml), and echo-Doppler measure of E/A ratio.

Missing Data

The presence of missing data can bias the results if the mean values of the predictive covariates for the missing values are different between the two levels for a factor. This would result in the means of the predictive factors for the observed covariates to be different between the two levels of the factors. Analysis of covariance adjusts for differences in the means of the baseline measure of the outcome and other

predictor covariates to estimate what the mean in each level of the factor would be had both groups had the same overall mean of the covariates in the model. This method is equivalent to multiple imputation of missing data with the covariates as predictors and infinite iterations.

A sensitivity analysis was performed on the one significant primary outcome, peak VO_2. The main effects of the interventions on peak VO_2 was that among the observed outcome data adjusting for baseline peak VO_2, gender, and beta blocker usage was that the mean value 1.29 ml/kg/min higher than the no diet groups. There was only 10% missing data; however if the mean of the no intervention groups were higher than the mean of missing intervention groups, could bias the results. A sensitivity analysis was conducted to see how much larger the mean of the missing data in the no intervention groups than the intervention groups needed to be in order to make the results non-significant. The mean of the 5 missing non-exercise patients would have to be greater than 6.30 ml/kg/min larger than the mean of the 5 missing exercise patients and the mean of the 4 missing non-diet patients would have to be 18.78 ml/kg/min larger than the mean of the 6 missing diet patients. None of these conditions were met.

Multiple Stepwise Regression

To see which variables were independent predictors of change in peak VO_2, a multiple stepwise regression predicting peak VO_2 on age, gender, change in total mass, change in fat mass, change in percent lean mass, change in thigh skeletal muscle/intermuscular fat ratio, change in LV mass, and change in CRP was conducted with a p-to-entry = 0.05. The results showed that gender and change in total mass were the only independent predictors of change in peak VO_2. Once these factors were adjusted for, the other variables were not significant to enter the model as an independent predictor.

Supplemental Details on Exercise Attendance and Progression

Participants completing Exercise and Exercise+Diet attended 84% and 91% of exercise sessions, respectively, and progressed from a median of 18 ± 5min at 2.7 ± 0.4 metabolic equivalent (MET) level and 19 ± 7 min at a 2.9 ± 0.3 MET level at week 1, respectively, to a median of 48 ± 10min at a 3.6 ± 1.2 MET level and 50 ± 11 min at a 4.1 ± 1.2 MET level at week 20, respectively.

Supplemental Details on Inflammation Biomarker Analysis Methods

IL-6 was measured using a high-sensitivity Quantikineâ immunoassay kit from R&D Systems, Minneapolis, MN (sensitivity>0.10 pg/mL, detection range=0.156-10.0 pg/mL). CRP was measured using an automated chemoluminescent immunoassay system (IMMULITE, Diagnostics Products Corporation, Los Angeles). This assay has a sensitivity of 0.10 μg/mL with a calibration range up to 150 μg/mL.

eTable 1. Baseline Characteristics of Randomized Group

Characteristic	Control (N=25)	Exercise (N=26)	Diet (N=24)	Exercise+Diet (N=25)
Age (years)	65.6 ± 4.8	67.5 ± 5.9	66.5 ± 4.9	66.3 ± 5.2
Women	20 (80%)	21 (81%)	20 (83%)	20 (80%)
White	16 (64%)	15 (58%)	11 (46%)	13 (52%)
Body Weight (kg)	105 ± 13	107± 24	99 ± 12.1	111 ± 19
BSA (m^2)	2.10 ± 0.14	2.09 ± 0.24	2.02 ± 0.16	2.15 ± 0.21
BMI (kg/m^2)	39.4 ± 5.6	39.9 ± 8.4	37.3 ± 3.6	40.7 ± 5.6
Body fat (%)	46 ± 7	45 ± 6	45 ± 7	46 ± 6
NYHA class				
II	17 (68%)	12 (46%)	16 (67%)	15 (60%)
III	8 (32%)	14 (54%)	8 (33%)	10 (40%)
Ejection fraction (%)	62.5 ± 5.5	60.7 ± 6.1	61.2 ± 7.0	60.0 ± 5.7
LV Mass (g)	210 ± 50	211 ± 67	222 ± 65	214 ± 61
Relative wall thickness	0.58 ± 0.10	0.58 ± 0.13	0.56 ± 0.13	0.57 ± 0.12
Diastolic filling pattern				
Normal	0 (0%)	1 (4%)	1 (4%)	0 (0%)
Impaired Relaxation	23 (92%)	22 (85%)	19 (83%)	23 (92%)
Pseudonormal	1 (4%)	3 (12%)	3 (13%)	2 (8%)
Restrictive	1 (4%)	0 (0%)	0 (0%)	0 (0%)
e' (cm/s)	5.9 ± 1.3	6.4 ± 1.2	6.2 ± 1.9	6.2 ± 1.5
E/ e' ratio	13.8 ± 3.7	12.6 ± 3.2	12.9 ± 4.3	13.1 ± 3.6
B-type natriuretic peptide (pg/ml)	21.9 (18.2, 26.5)	23.6 (19.4, 39.4)	21.1 (17.6, 26.4)	27.4 (19.1, 37.8)
Current atrial fibrillation	0 (0%)	1 (4%)	1 (4%)	0 (0%)
History of diabetes mellitus	9 (36%)	10 (38%)	5 (21%)	11 (44%)
History of hypertension	24 (96%)	25 (96%)	23 (96%)	23 (92%)
Systolic BP (mmHg)	137 ± 17	136 ± 16	134 ± 14	137 ± 16
Diastolic BP (mmHg)	77 ± 7	78 ± 8	76 ± 7	79 ± 10
Current medications				
ACE-inhibitors	8 (32%)	11 (42%)	9 (38%)	9 (36%)
Diuretics	20 (80%)	21 (81%)	18 (75%)	17 (68%)
Beta-blockers	11 (44%)	10 (38%)	9 (38%)	10 (40%)
Calcium Antagonists	7 (28%)	10 (38%)	10 (42%)	8 (32%)
Nitrates	4 (16%)	1 (4%)	2 (8%)	2 (8%)
ARB's	8 (32%)	12 (46%)	8 (33%)	7 (28%)
Peak VO_2 (ml/kg/min)	14.0 ± 2.1	14.4 ± 2.4	14.8 ± 2.4	14.7 ± 3.3
Peak VO_2 % of predicted	56.7 ± 8.7	57.5 ± 9.8	59.1 ± 9.6	58.8 ± 13.2

Peak VO_2 (ml/min)	1463 ± 213	1505 ± 332	1455 ± 318	1608 ± 361
Peak RER	1.14 ± 0.08	1.10 ± 0.06	1.11 ± 0.10	1.14 ± 0.08
Exercise time (min)	10.1 ± 2.3	9.7 ± 2.5	10.4 ± 2.0	10.2 ± 2.8
6 minute walk (feet)	1345 ± 213	1346 ± 275	1392 ± 190	1327 ± 270
6 minute walk % of predicted	72.8 ± 11.5	72.9 ± 14.9	75.4 ± 10.3	71.9 ± 14.6

Data are presented as mean ± SD or count (%), except for B-type natriuretic peptide which is expressed as median (25^{th},75^{th} percentile). Abbreviations: BSA, body surface area; BMI, body mass index; NYHA, New York Heart Association HF class; LV, left ventricular; EDV, end diastolic volume; e', early mitral annulus velocity (septal); E, E-wave velocity; BP, blood pressure; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; VO_2, oxygen consumption; RER, respiratory exchange ratio. Diastolic filling pattern determined according to ASE (American Society of Echocardiography) criteria. Peak VO_2 and 6 minute walk % of predicted as compared to 60 healthy age and gender-matched sedentary controls (Stehle et al, J Gerontol Med Sci 2012; 11: 1212-1218).

eTable 2. Exercise Performance and Quality of Life by Randomized Group

Variable	Overall Baseline	Control (N=25)	Exercise (N=26)	Diet (N=24)	Exercise+Diet (N=25)
Primary Outcomes	**Mean ± SD**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**
Peak VO_2 (ml/kg/min)	14.5 ± 2.6	14.1 (13.5, 14.7)	15.5 (15.1, 15.9)	15.5 (15.1, 15.9)	16.6 (16.0, 17.2)
MLHF Total Score	29 ± 20	21 (15, 27)	22 (16, 28)	17 (11, 23)	14 (8, 20)
Exploratory Outcomes					
Exercise Performance					
Peak VO_2 (ml/kglean/min)	28.0 ± 4.3	27.3 (26.3, 28.3)	30.0 (28.8, 31.2)	29.1 (28.1, 30.1)	30.5 (29.3, 31.7)
Peak VO_2 (ml/kgleglean/min)	88.5 ± 15.4	86.6 (83.3, 89.9)	93.3 (89.6, 97.0)	91.5 (88.4, 94.6)	97.1 (93.4, 100.8)
Peak VO_2 (ml/cm^2muscle/min)	12.7 ± 2.2	12.3 (11.9, 12.7)	13.6 (13.2, 14.0)	13.2 (12.8, 13.6)	14.0 (13.6, 14.4)
Peak VO_2 (ml/min)	1515 ± 321	1465 (1420, 1510)	1574 (1529, 1619)	1501 (1458, 1544)	1573 (1526, 1620)
VO_2 reserve (ml/min)	1164 ± 289	1121 (1068, 1174)	1237 (1188, 1286)	1199 (1150, 1248)	1276 (1219, 1333)
Exercise Time (min)	10.2 ± 2.4	10.2 (9.6, 10.8)	12.0 (11.4, 12.6)	11.6 (11.0, 12.2)	13.8 (13.2, 14.4)
Workload (METS)	5.8 ± 1.2	6.0 (5.6, 6.4)	6.7 (6.3, 7.1)	6.6 (6.2, 7.0)	7.5 (7.1, 7.9)
Peak HR (bpm)	139 ± 18	137 (133, 141)	135 (131, 139)	135 (131, 139)	137 (133, 141)
Peak SBP (mmHg)	178 ± 19	171 (165, 177)	173 (167, 179)	172 (166, 178)	169 (163, 175)
Peak DBP (mmHg)	78 ± 9	80 (78, 82)	76 (74, 78)	74 (72, 76)	71 (69, 73)
Peak RER	1.12 ± 0.08	1.10 (1.08, 1.12)	1.14 (1.12, 1.16)	1.14 (1.12, 1.16)	1.15 (1.13, 1.17)
VAT (ml/kg/min)	9.7 ± 1.9	9.7 (9.1, 10.3)	10.1 (9.5, 10.7)	9.9 (9.3, 10.5)	10.4 (9.8, 11.0)
VE/VCO2 Slope	29.6 ± 3.9	29.9 (28.7, 31.1)	29.0 (27.8, 30.2)	29.4 (28.4, 30.4)	29.4 (28.2, 30.6)
6 Minute walk (feet)	1351 ± 226	1372 (1327, 1417)	1437 (1390, 1484)	1420 (1377, 1463)	1563 (1518, 1608)
Leg Power (watts)	111 ± 51	114 (102, 126)	109 (97, 121)	122 (110, 134)	122 (108, 136)
Leg muscle quality(w/cm^2)	0.90 ± 0.32	0.90 (0.78, 1.02)	0.91 (0.79, 1.03)	1.09 (0.99, 1.19)	1.02 (0.90, 1.14)
Quality of Life					
KCCQ Total Score	62 ± 16	69 (63, 75)	71 (67, 75)	77 (73, 81)	79 (75, 84)
SF-36 PCS	37 ± 9	41 (37, 45)	40 (38, 42)	44 (42, 46)	45 (41, 49)
NYHA Class	2.4 ± 0.5	2.4 (2.2, 2.6)	1.8 (1.6, 2.0)	1.8 (1.6, 2.0)	1.7 (1.5, 1.9)

Data are presented as Overall baseline mean ± SD and Least Square Means (LSMean) of follow-up visit (95% CI). Abbreviations: FU, Follow-up; SD, standard deviation; SE, standard error; VO_2, oxygen consumption; SBP, systolic blood pressure; DBP, diastolic BP; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; VE, ventilatory equivalents; VCO_2, carbon dioxide production; MLHF, Minnesota Living With Heart Failure Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-36PCS, Medical Outcomes Short Form 36 Health Survey Physical Component Score; NYHA, New York Heart Association HF Class. MLHF, score range is 0–105, higher scores indicate worse HF-related QOL. KCCQ; range 0-100; higher scores indicate better QOL. SF-36; range 0-100, average is 50; higher scores indicate better QOL. Peak VO_2 per kg of lean and per kg of leglean measured by DXA; cm^2 muscle is area of thigh muscle measured by MRI. Leg muscle quality = leg power / thigh muscle area.

eTable 3. Body Composition, Cardiac Function and Vascular Function

Variable	Overall Baseline	Control (N=25)	Exercise (N=26)	Diet (N=24)	Exercise+Diet (N=25)
Body composition	**Mean ± SD**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**	**FU LSMean (95% CI)**
Weight (kg)	106 ± 18	105 (103, 107)	102 (100, 104)	99 (97, 101)	95 (93, 97)
DXA Measurements					
Total non-bone lean (kg)	53 ± 9	53 (53, 53)	52 (50, 54)	50 (50, 50)	50 (48, 52)
Total fat (kg)	47 ± 10	47 (45, 49)	45 (43, 47)	42 (40, 44)	40 (38, 42)
Total non-bone lean (%)	52 ± 6	52 (52, 52)	52 (52, 52)	54 (54, 54)	55 (55, 55)
Total fat (%)	45 ± 6	46 (46, 46)	45 (45, 45)	44 (44, 44)	43 (43, 43)
MRI measurements					
Thigh subcut fat (cm^2)	165 ± 78	164 (158, 170)	155 (149, 161)	143 (137, 149)	144 (138, 150)
Thigh skeletal muscle (cm^2)	122 ± 26	121 (117, 125)	120 (118, 122)	115 (113, 117)	114 (112, 116)
Thigh IM fat (cm^2)	25 ± 9	25 (23, 27)	25 (23, 27)	25 (23, 27)	24 (22, 26)
Thigh SM/IM fat ratio	5.4 ± 2.4	5.5 (5.1, 5.9)	5.4 (5.0, 5.8)	5.4 (5.0, 5.8)	5.8 (5.4, 6.2)
Abd subcut fat (cm^2)	378 ± 152	374 (358, 390)	371 (355, 387)	324 (310, 338)	318 (302, 334)
Abd visceral fat (cm^2)	213 ± 108	215 (203, 227)	206 (194, 218)	185 (175, 195)	174 (162, 186)
Epicardial fat (cm^3)	36 ± 17	35 (31, 39)	38 (34, 42)	37 (33, 41)	38 (32, 42)
Pericardial fat (cm^3)	64 ± 41	58 (52, 64)	59 (53, 65)	59 (53, 65)	52 (46, 58)
Cardiac function					
MRI measurements					
Mass (g)	95 ± 19	92 (88, 96)	98 (94, 102)	91 (87, 95)	91 (87, 95)
End diastolic volume (ml)	122 ± 25	119 (113, 125)	125 (117, 133)	127 (121, 133)	120 (112, 128)
Ejection fraction (%)	61 ± 6	63 (61, 65)	61 (59, 63)	60 (58, 62)	62 (60, 64)
Echo-Doppler measurements					
LV Mass (g)	212 ± 59	209 (199, 219)	212 (202, 222)	207 (197, 217)	214 (204, 224)
Relative wall thickness	0.57 ± 0.11	0.58 (0.56, 0.60)	0.57 (0.55, 0.59)	0.55 (0.53, 0.57)	0.53 (0.51, 0.55)
LA diameter (cm)	4.0 ± 0.5	4.0 (3.2, 4.8)	4.0 (3.2, 4.8)	4.0 (3.2, 4.8)	4.0 (3.2, 4.8)
Cardiac index	4.9 ± 1.1	4.8 (4.4, 5.2)	4.6 (4.2, 5.0)	4.7 (4.3, 5.1)	4.8 (4.4, 5.2)
E/A ratio	0.87 ± 0.20	0.81 (0.73, 0.89)	0.86 (0.78, 0.94)	0.97 (0.89, 1.05)	0.90 (0.82, 0.98)
e' (cm/s)	6.2 ± 1.5	6.3 (5.7, 6.9)	6.1 (5.5, 6.7)	6.3 (5.7, 6.9)	6.2 (5.6, 6.8)
E/ e' ratio	13.0 ± 3.6	12.2 (10.6, 13.8)	13.1 (11.7, 14.5)	13.6 (12.2, 15.0)	13.0 (11.6, 14.4)
Vascular function					
Arterial stiffness (cm/s)	1047 ± 291	1041 (941, 1141)	1011 (913, 1109)	977 (877, 1077)	977 (877, 1077)

Data are presented as Overall baseline mean ± SD and Least Square Means (LSMeans) at follow-up visit (95% CI). Abbreviations: FU, Follow-up; SD, standard deviation; SE, standard error; DXA, dual x-ray absorptiometry; MRI, magnetic resonance imaging; subcut, subcutaneous; IM, intermuscular; SM, skeletal muscle; Abd, abdominal; LA, left atrial; E/A, early to atrial filling velocity; e', early mitral annulus velocity (septal). Relative wall thickness is the ratio of wall thickness divided by chamber size. Cardiac output measured by echo-Doppler LV outflow tract technique. Arterial stiffness determined using pulse wave velocity from carotid to femoral artery.

eTable 4. Additional Resting Left Ventricular and Echo-Doppler Characteristics and Blood-based Markers

Variable	Overall Baseline	Control (N=25)	Exercise (N=26)	Diet (N=24)	Exercise+Diet (N=25)
	Mean ± SD	FU LSMean (95% CI)	FU LSMean (95% CI)	FU LSMean (95% CI)	FU LSMean (95% CI)
Left Ventricular (MRI)					
Mass/EDV ratio	0.79 ± 0.14	0.78 (0.74, 0.82)	0.80 (0.76, 0.84)	0.74 (0.70, 0.78)	0.77 (0.73, 0.81)
ESV (ml)	48 ± 15	45 (41, 49)	50 (46, 54)	51 (47, 55)	45 (41, 49)
SV (ml)	74 ± 14	74 (70, 78)	75 (71, 79)	76 (72, 80)	74 (70, 78)
Echo-doppler					
E-wave velocity (cm/s)	77 ± 17	74 (68, 80)	77 (71, 83)	80 (76, 84)	79 (73, 85)
A-wave velocity (cm/s)	90 ± 19	90 (84, 96)	93 (89, 97)	87 (81, 93)	90 (84, 96)
E decel time (ms)	244 ± 54	255 (233, 277)	258 (238, 278)	233 (213, 253)	251 (231, 271)
Lipids					
Total Cholesterol (mg/dL)	171 ± 39	173 (163, 183)	175 (165, 185)	165 (155, 175)	154 (144, 164)
LDL (mg/dL)	96 ± 30	99 (91, 107)	100 (92, 108)	91 (83, 99)	83 (75, 91)
HDL (mg/dL)	49 ± 14	49 (45, 53)	50 (48, 52)	48 (46, 50)	50 (46, 54)
Inflammation Biomarkers					
hsCRP (µg/L)	8.3 ± 8.9	8.3 (6.3, 10.3)	9.3 (7.3, 11.3)	6.9 (4.9, 8.9)	5.1 (2.9, 7.3)
IL-6 (pg/ml)	6.7 ± 24.8	4.5 (3.7, 5.3)	4.8 (4.2, 5.4)	3.6 (3.0, 4.2)	4.0 (3.2, 4.8)
Fasting Glucose (mg/dL)	118 ± 40	118 (108, 128)	114 (106, 122)	112 (102, 122)	98 (88, 108)
B-type natriuretic peptide (pg/ml)	31 ± 26	27 (23, 31)	28 (24, 32)	28 (24, 32)	31 (25, 37)

Data are presented as Overall baseline mean ± SD and Least Square Means (LSMeans) at follow-up visit (95% CI). Abbreviations: FU, Follow-up; SD, standard deviation; SE, standard error; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; decel, deceleration; LDL, low-density lipoprotein; CRP, C-Reactive Protein; IL, interleukin.

Figure Legends

eFigure 1

Adjusted individual changes and means with 95% CIs at the 20-week follow-up relative to baseline of exploratory measures by factorial group of exercise capacity and quality of life: Exercise Time (panel A); 6-minute walk distance (6MWD, panel B); Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ,; panel C); and 36-Item Short Form Health Survey Physical Component Score (SF-36, panel D). KCCQ; range 0-100; higher scores indicate better QOL. SF-36; range 0-100, average is 50; higher scores indicate better QOL The p-values represent comparison of least square means of the outcome measure groups following adjustment for baseline values for gender and beta blocker use.

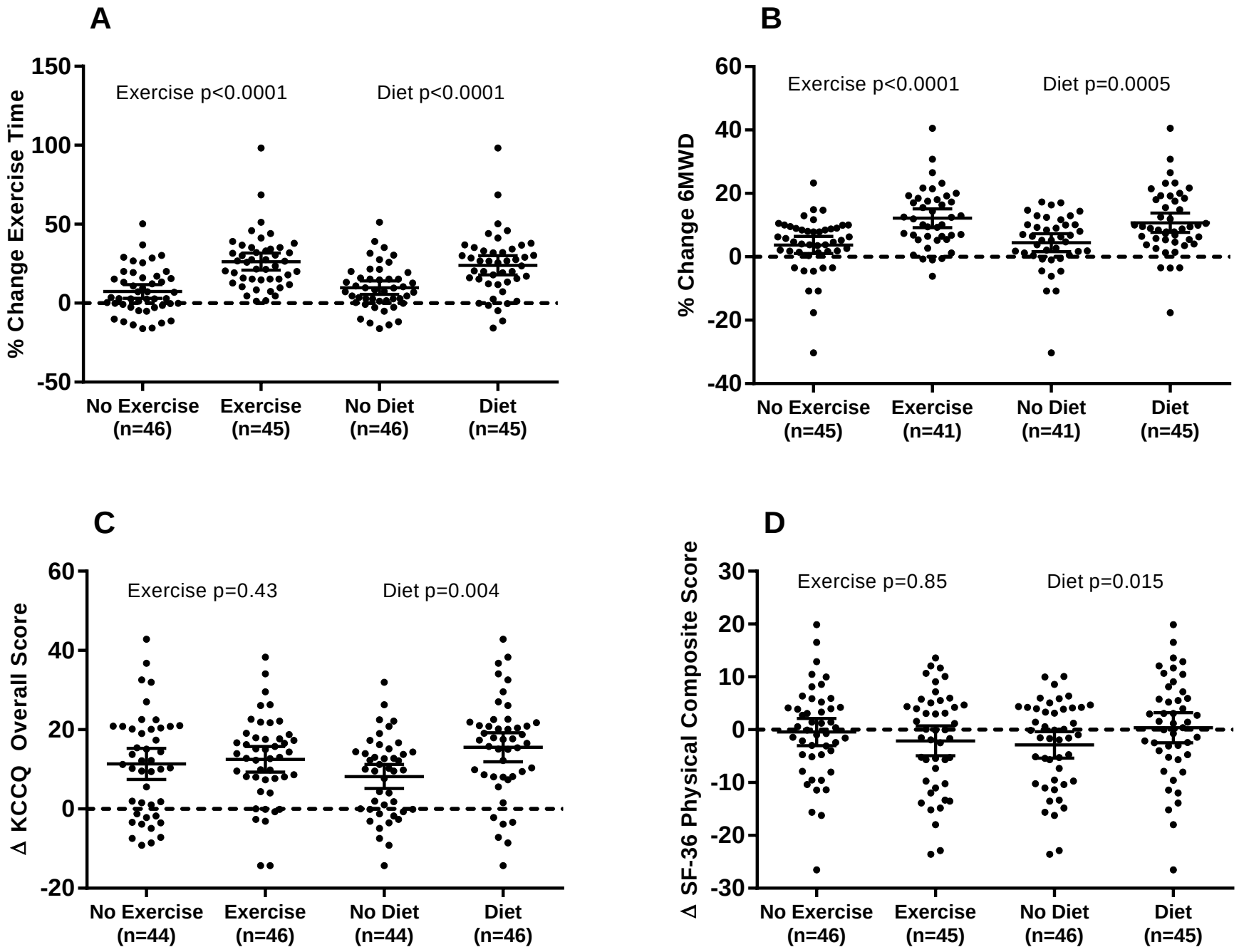
eFigure 2

Weight change (follow-up weight – baseline weight) by randomized group (panel A) and by factorial analysis group (panel B). Each symbol represents one participant; horizontal line represents group mean, bars represent 95% CIs. The p-values shown in Panel B represent comparison of least square means of the outcome measure by factorial group following adjustment for baseline values for gender and beta blocker use.

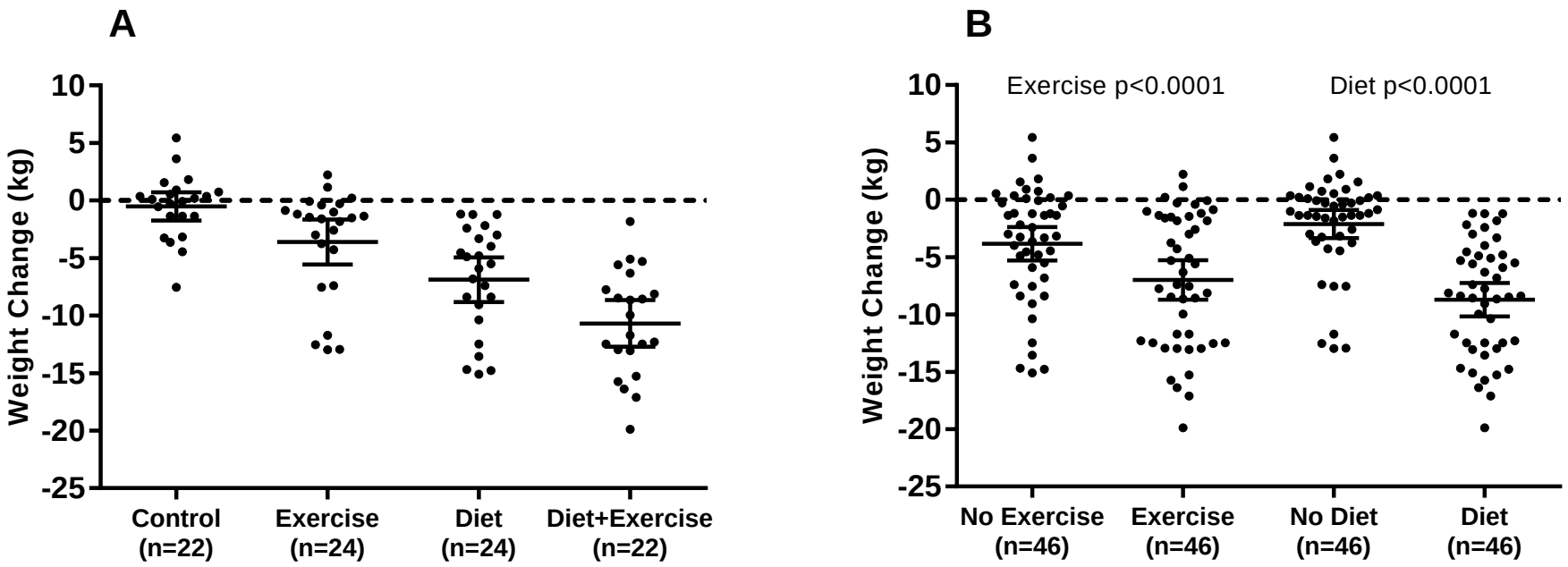
eFigure 3

Association between the change in the primary exercise capacity outcome, peak VO_2, and the change in total body mass (panel A), the change in fat mass (panel B), the change in percent lean mass (panel C), and the change in skeletal muscle to intermuscular fat ratio (SM/IMF, panel D). Each symbol represents individual changes displayed by randomized group: Control in open circles; Diet in closed circles; Exercise in open triangles; Diet+Exercise in closed triangles. Trendline represents linear regression between variables. The r and p-values shown are unadjusted. Of note, with the change in exercise time, a weight-independent measure of exercise capacity, as the dependent variable, the r and p-values are: change in total body mass ($r=-0.59$, $p<0.001$), change in fat mass ($r=-0.49$, $p<0.001$), change in percent lean mass ($r=0.34$, $p=0.002$), and change in SM/IMF ratio ($r=0.36$, $p=0.001$).

eFigure 1. Changes in exercise and quality of life outcomes by factorial group



eFigure 2. Weight change by randomized group and by factorial group



eFigure 3. Associations with the change in peak $\dot{V}O_2$