

Supplement Table 1. Baseline characteristics by completers and non-completers of the 12-month assessments

	Completers	Non-completers	P value
	(n = 399)	(n = 39)	
Intervention assignment, No. of participants			
Control	80	7	0.720
Exercise	106	11	
Diet	105	13	
Diet + Exercise	108	8	
Age, years			
Mean (SD)	58.0 (5.1)	57.5 (4.4)	0.538
Non-Hispanic white			
N, %	340 (85.2)	32 (82.1)	0.598
College degree			
N, %	262 (65.7)	24 (61.5)	0.605
Married or have partner			
N, %	254 (63.8)	24 (61.5)	0.777
Ever smoked*			
N, %	161 (40.4)	20 (51.3)	0.186
Body mass index, kg/m²			
Mean (SD)	30.8 (4.0)	31.9 (3.8)	0.081
Waist circumference, cm			
Mean (SD)	94.1 (9.9)	98.7 (11.3)	0.007
Statin users			
N, %	70 (17.5)	3 (7.7)	0.115
NSAID users			
N, %	139 (34.8)	18 (46.2)	0.159
Aerobic fitness, mL/kg/min			
Mean (SD)	23.0 (4.1)	22.3 (2.9)	0.166
Physical activity, min/week			
Mean (SD)	32.8 (44.3)	28.5 (36.9)	0.558
Calorie intake, kcal/day			
Mean (SD)	1919 (615)	2107 (830)	0.185
Percent calorie intake from fat, %			
Mean (SD)	34.2 (6.9)	35.3 (6.7)	0.344
Inflammatory biomarkers			
High-sensitivity C-reactive protein, mg/L			
Mean (SD)	3.55 (3.58)	3.71 (3.76)	0.787
Serum amyloid A, mg/L			
Mean (SD)	6.42 (4.96)	7.51 (6.90)	0.499
Interleukin-6, pg/mL			
Mean (SD)	1.73 (1.56)	2.05 (1.58)	0.079
Leukocytes, x10⁹/L			
Mean (SD)	5.86 (1.35)	5.85 (1.19)	0.885
Neutrophils, x10⁹/L			
Mean (SD)	3.42 (1.03)	3.40 (0.98)	0.976

SD: standard deviation, NSAID: non-steroidal anti-inflammatory drug.

*All study participants were currently non-smokers

P values comparing completers (participants who completed 12-months assessments) vs. non-completers (participants who did not complete 12-months assessments).

T-test was used for continuous variables. Chi-test was used for categorical variables.

There were no differences between completers and non-completers by group assignment, baseline characteristics or inflammatory biomarkers except for waist circumference. Based on our understanding of the drop-out reasons (Figure 1), the follow-up outcomes did not appear to have a non-ignorable missing data mechanism (informative missingness). From these reasons, we used multiple imputation for missing data.

Supplement Table 2. Intervention effects on inflammatory biomarkers (excluding CRP outliers)

	Control (N=87)	Exercise (N=112)		Diet (N=117)		Diet + Exercise (N=114)	
	Geometric means (95% CI)	Geometric means (95% CI)	P value	Geometric means (95% CI)	P value	Geometric means (95% CI)	P value
Hs-CRP, mg/L							
Baseline	1.90 (1.50 to 2.40)	2.41 (1.95 to 2.98)		2.53 (2.05 to 3.13)		2.13 (1.71 to 2.64)	
12 months	2.01 (1.81 to 2.24)	2.19 (1.99 to 2.41)		1.71 (1.55 to 1.88)		1.27 (1.15 to 1.40)	
$\Delta_{12 \text{ months}}$ vs. control							
Absolute change	---	-0.32 (-0.65 to 0.01)	P _C =0.064 P _D <0.001	-0.91 (-1.29 to -0.53)	P _C <0.001 P _E <0.001	-0.90 (-1.25 to -0.54)	P _C <0.001 P _D =0.207
Percent change, %	---	-14.5 (-27.6 to 0.93)	P _{D+E} <0.001	-36.3 (-46.7 to -23.9)	P _{D+E} =0.207	-43.7 (-53.6 to -31.6)	P _E <0.001

Hs-CRP: high-sensitivity C-reactive protein, CI: confidence interval.

Hs-CRP outliers (≥ 20.0 mg/L, above 99%tertile; N=5 in exercise, N=1 in diet, N=2 in diet+exercise) were excluded from analysis.

P_C: p-values for comparing the 12-month changes vs. Control group, P_E: p-values for comparing the 12-month changes vs. Exercise group, P_D: p-values for comparing the 12-month changes vs. Diet group, P_{D+E}: p-values for comparing the 12-month changes vs.

Diet+Exercise group.

P-values <0.008 are considered significant due to multiple comparisons (Bonferroni correction): (1) Exercise vs. Control, (2) Diet vs. Control, (3) Diet+Exercise vs. Control, (4) Exercise vs. Diet, (5) Exercise vs. Diet+Exercise, and (6) Diet vs. Diet+Exercise.

All models were adjusted for randomization strata (i.e., baseline BMI [$<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$] and race/ethnicity [White, Black, and others]) and age.

Supplement Table 3. 12 months changes in inflammatory measures stratified by weight loss (excluding CRP outliers)

	Exercise				Diet				Diet + Exercise			
	$\Delta_{12\text{ months vs. control}}$				$\Delta_{12\text{ months vs. control}}$				$\Delta_{12\text{ months vs. control}}$			
	N	Absolute	Percent	P	N	Absolute	Percent	P	N	Absolute	Percent	P
Hs-CRP, mg/L												
Weight loss<5%	83	-0.21	-8.2	0.289	42	-0.08	-2.4	0.696	27	-0.19	-11.8	0.381
Weight loss \geq 5%	29	-0.63	-25.1	0.005	75	-1.23	-49.5	<0.001	87	-1.05	-51.6	<0.001

Hs-CRP: high-sensitivity C-reactive protein.

Hs-CRP outliers (≥ 20.0 mg/L, above 99%tertile; N=5 in exercise, N=1 in diet, N=2 in diet+exercise) were excluded from analysis.

P values testing differences in changes from baseline to 12 months in inflammatory biomarkers compared to controls.

All models were adjusted for randomization strata (i.e., baseline BMI [$<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$] and race/ethnicity [White, Black, and others]) and age.

Supplement Table 4. Caloric restriction diet effects on inflammatory biomarkers

	No caloric restriction diet (Exercise & Control) (N=201)	Caloric restriction diet (Diet & Diet+exercise) (N=234)	
	Geometric means (95% CI)	Geometric means (95% CI)	P value
High-sensitivity CRP, mg/L			
Baseline	2.22 (1.92 to 2.56)	2.35 (2.08 to 2.66)	
12 months	2.06 (1.76 to 2.41)	1.39 (1.20 to 16.0)	
$\Delta_{12\text{ months}}$ vs. no diet			<0.001
Absolute change	---	-0.80 (-1.10 to -0.50)	
Percent change, %	---	-35.7 (-44.2 to -25.8)	
Serum amyloid A, mg/L			
Baseline	5.30 (4.83 to 5.81)	5.09 (4.69 to 5.53)	
12 months	5.15 (4.60 to 5.77)	3.93 (3.56 to 4.35)	
$\Delta_{12\text{ months}}$ vs. no diet			<0.001
Absolute change	---	-1.01 (-1.59 to -0.43)	
Percent change	---	-20.5 (-29.2 to -10.6)	
Interleukin-6, pg/ml			
Baseline	1.46 (1.34 to 1.59)	1.43 (1.33 to 1.54)	
12 months	1.42 (1.29 to 1.56)	1.08 (1.01 to 1.17)	
$\Delta_{12\text{ months}}$ vs. no diet			<0.001
Absolute change	---	-0.31 (-0.44 to -0.18)	
Percent change	---	-21.5 (-28.5 to -13.8)	
Leukocyte count, x 10⁹ /L			
Baseline	5.63 (5.45 to 5.81)	5.78 (5.62 to 5.95)	
12 months	5.47 (5.29 to 5.65)	5.28 (5.12 to 5.44)	
$\Delta_{12\text{ months}}$ vs. no diet			<0.001
Absolute change	---	-0.34 (-0.51 to -0.18)	
Percent change	---	-5.8 (-8.6 to -2.9)	
Neutrophil count, x 10⁹ /L			
Baseline	3.19 (3.06 to 3.33)	3.34 (3.22 to 3.46)	
12 months	3.10 (2.96 to 3.25)	2.94 (2.83 to 3.06)	
$\Delta_{12\text{ months}}$ vs. no diet			<0.001
Absolute change	---	-0.30 (-0.44 to -0.16)	
Percent change	---	-8.8 (-12.8 to -4.7)	

CRP: C-reactive protein, CI: confidence interval.

P-values for comparing the 12-month changes in inflammatory biomarkers between caloric restriction diet (Diet and Diet+Exercise) and no caloric restriction diet (Exercise and Control).

All models were adjusted for randomization strata (i.e., baseline BMI [$<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$] and race/ethnicity [White, Black, and others]) and age.

Supplement table 5. Exercise effects on inflammatory biomarkers

	No exercise (Diet & Control) (N=201)	Exercise (Exercise & Diet+exercise) (N=234)	
	Geometric means (95% CI)	Geometric means (95% CI)	P value
High-sensitivity CRP, mg/L			
Baseline	2.27 (1.97 to 2.62)	2.31 (2.04 to 2.61)	
12 months	1.70 (1.47 to 1.97)	1.64 (1.41 to 1.91)	
$\Delta_{12\text{ months}}$ VS. no exercise			0.437
Absolute change	---	-0.10 (-0.39 to 0.19)	
Percent change, %	---	-5.5 (-18.0 to 9.0)	
Serum amyloid A, mg/L			
Baseline	5.32 (4.86 to 5.81)	5.07 (4.66 to 5.52)	
12 months	4.32 (3.91 to 4.77)	4.59 (4.11 to 5.12)	
$\Delta_{12\text{ months}}$ VS. no exercise			0.054
Absolute change	---	0.52 (-0.01 to 1.04)	
Percent change	---	11.4 (-0.2 to 24.3)	
Interleukin-6, pg/ml			
Baseline	1.47 (1.36 to 1.59)	1.42 (1.32 to 1.53)	
12 months	1.26 (1.16 to 1.36)	1.21 (1.11 to 1.31)	
$\Delta_{12\text{ months}}$ VS. no exercise			0.851
Absolute change	---	0.00 (-0.13 to 0.13)	
Percent change	---	-0.9 (-9.9 to 9.0)	
Leukocyte count, x 10⁹ /L			
Baseline	5.72 (5.54 to 5.91)	5.70 (5.54 to 5.86)	
12 months	5.40 (5.23 to 5.58)	5.33 (5.17 to 5.50)	
$\Delta_{12\text{ months}}$ VS. no exercise			0.551
Absolute change	---	-0.05 (-0.22 to 0.13)	
Percent change	---	-0.9 (-3.9 to 2.2)	
Neutrophil count, x 10⁹ /L			
Baseline	3.27 (3.14 to 3.41)	3.27 (3.15 to 3.39)	
12 months	3.00 (2.88 to 3.13)	3.03 (2.90 to 3.16)	
$\Delta_{12\text{ months}}$ VS. no exercise			0.735
Absolute change	---	0.03 (-0.11 to 0.17)	
Percent change	---	0.8 (-3.6 to 5.4)	

CRP: C-reactive protein, CI: confidence interval.

P-values for comparing the 12-month changes in inflammatory biomarkers between exercise (Exercise and Diet+Exercise) and no exercise (Diet and Control).

All models were adjusted for randomization strata (i.e., baseline BMI [$<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$] and race/ethnicity [White, Black, and others]) and age.

Supplement Table 6. Intervention effects on inflammatory biomarkers (available data analysis)

	Control (N=87)	Exercise (N=117)		Diet (N=118)		Diet + Exercise (N=116)	
	Geometric means (95% CI)	Geometric means (95% CI)	P value	Geometric means (95% CI)	P value	Geometric means (95% CI)	P value
Hs-CRP, mg/L							
Baseline	1.89 (1.52 to 2.34)	2.51 (2.08 to 3.03)		2.57 (2.12 to 3.10)		2.12 (1.76 to 2.57)	
12 months	2.03 (1.60 to 2.57)	2.41 (1.95 to 2.97)		1.68 (1.35 to 2.08)		1.30 (1.05 to 1.60)	
$\Delta_{12\text{ months}}$ vs. control							
Absolute change	---	-0.20 (-0.60 to 0.20)	P _C =0.369 P _D <0.001 P _{D+E} <0.001	-1.09 (-1.48 to -0.70)	P _C <0.001 P _E <0.001 P _{D+E} =0.365	-0.99 (-1.35 to -0.64)	P _C <0.001 P _D =0.365 P _E <0.001
Percent change, %	---	-8.2 (-23.8 to 10.7)		-40.9 (-50.3 to -29.7)		-46.0 (-55.6 to -34.2)	
SAA, mg/L							
Baseline	5.22 (4.50 to 6.06)	5.19 (4.56 to 5.92)		5.19 (4.55 to 5.93)		4.80 (4.20 to 5.48)	
12 months	5.21 (4.38 to 6.21)	5.65 (4.84 to 6.60)		3.88 (3.31 to 4.55)		4.06 (3.47 to 4.75)	
$\Delta_{12\text{ months}}$ vs. control							
Absolute change	---	0.65 (-0.25 to 1.54)	P _C =0.156 P _D <0.001 P _{D+E} =0.002	-1.12 (-1.74 to -0.49)	P _C <0.001 P _E <0.001 P _{D+E} =0.212	-0.63 (-1.29 to 0.03)	P _C =0.021 P _D =0.212 P _E =0.002
Percent change	---	12.8 (-4.5 to 33.1)		-22.2 (-31.4 to -11.8)		-15.0 (-25.9 to 2.4)	
Interleukin-6, pg/ml							
Baseline	1.43 (1.26 to 1.62)	1.49 (1.34 to 1.67)		1.50 (1.34 to 1.68)		1.36 (1.22 to 1.52)	
12 months	1.54 (1.35 to 1.75)	1.55 (1.38 to 1.73)		1.24 (1.10 to 1.39)		1.09 (0.97 to 1.22)	
$\Delta_{12\text{ months}}$ vs. control							
Absolute change	---	-0.05 (-0.23 to 0.13)	P _C =0.521 P _D <0.001 P _{D+E} <0.001	-0.38 (-0.57 to -0.20)	P _C <0.001 P _E <0.001 P _{D+E} =0.677	-0.36 (-0.53 to -0.19)	P _C <0.001 P _D =0.677 P _E <0.001
Percent change	---	-3.9 (-15.0 to 8.6)		-24.6 (-33.7 to -14.3)		-26.5 (-35.1 to -16.9)	
Leukocytes, x10⁹/L							
Baseline	5.44 (5.17 to 5.73)	5.57 (5.32 to 5.83)		5.72 (5.46 to 5.99)		5.60 (5.35 to 5.86)	
12 months	5.40 (5.11 to 5.71)	5.53 (5.26 to 5.81)		5.35 (5.09 to 5.63)		5.11 (4.87 to 5.37)	
$\Delta_{12\text{ months}}$ vs. control							
Absolute change	---	-0.02 (-0.28 to 0.24)	P _C =0.807 P _D =0.011 P _{D+E} =0.004	-0.34 (-0.59 to -0.09)	P _C =0.011 P _E =0.011 P _{D+E} =0.275	-0.44 (-0.69 to -0.19)	P _C <0.001 P _D =0.275 P _E =0.004
Percent change	---	-0.6 (-5.1 to 4.1)		-5.7 (-9.9 to -1.4)		-7.9 (-12.0 to -3.5)	
Neutrophils, x10⁹/L							
Baseline	3.02 (2.82 to 3.23)	3.13 (2.95 to 3.32)		3.25 (3.06 to 3.45)		3.17 (2.99 to 3.37)	
12 months	3.03 (2.82 to 3.27)	3.14 (2.94 to 3.35)		2.94 (2.75 to 3.14)		2.89 (2.70 to 3.08)	
$\Delta_{12\text{ months}}$ vs. control							
Absolute change	---	0.00 (-0.21 to 0.20)	P _C =0.929 P _D <0.001 P _{D+E} <0.001	-0.33 (-0.55 to -0.12)	P _C =0.003 P _E <0.001 P _{D+E} =0.956	-0.31 (-0.52 to -0.10)	P _C =0.003 P _D =0.956 P _E <0.001
Percent change	---	-0.6 (-5.1 to 4.1)		-5.7 (-9.9 to -1.4)		-7.8 (-12.0 to -3.5)	

Hs-CRP: high-sensitivity C-reactive protein, SAA: serum amyloid A, CI: confidence interval. P_C: p-values for comparing the 12-month changes vs. Control group, P_E: p-values for comparing the 12-month changes vs. Exercise group, P_D: p-values for comparing the 12-month changes vs. Diet group, P_{D+E}: p-values for comparing the 12-month changes vs. Diet+Exercise group.

P-values <0.008 are considered significant due to multiple comparisons (Bonferroni correction): (1) Exercise vs. Control, (2) Diet vs. Control, (3) Diet+Exercise vs. Control, (4) Exercise vs. Diet, (5) Exercise vs. Diet+Exercise, and (6) Diet vs. Diet+Exercise. All models were adjusted for randomization strata (i.e., baseline BMI [$<30\text{kg/m}^2$, $\geq 30\text{kg/m}^2$] and race/ethnicity [White, Black, and others]) and age.