Supplemental Material

Expanded Methods

Physiological and Biochemical Methods

For intraperitoneal glucose tolerance tests (GTTs), mice were fasted for 11 h (2200 to 0900 h) with free access to drinking water. A baseline blood sample was collected from the tails of fully conscious mice, followed by intraperitoneal injection of glucose (2 g glucose/kg body weight), and blood was taken from the tails for glucose measurements at 0, 15, 30, 60, and 120 min[51]. The assessment of fat and lean mass was performed using an Echo-MRI-3-in-1.

Comprehensive Lab Animal Monitoring System

The Comprehensive Lab Animal Monitoring System (Oxymax Opto-M3; Columbus Instruments) was used to measure activity level, volume of O_2 consumption, volume of CO_2 production, and heat production. Total energy expenditure of mice was calculated as described previously[52].

Supplemental Table I. Exercise paradigm.

Weeks	Incline (%)	Total Daily Time (min)	Number of Sets	Fast Pace (m/min)	Recovery Pace (m/min)
1	5	40	8	18	10
2	10	50	10	20	10
3	15	60	12	22	11
4	20	70	14	24	11
5	20	80	16	26	12
6	20	80	16	28	12
7	20	80	16	30	13
8	20	80	18	32	13

Supplemental Table II. Echocardiography parameters.

	Heart Rate	Diameter (Systole)	Diameter (Diastole)	Volume (Systole)	Volume (Diastole)	Stroke Volume	Ejection Fraction	Cardiac Output	LV Mass	LVPW (Systole)	LVPW (Diastole)
Sham-Sedentary	479.5±23.3	2.66±0.14	3.9±0.04	26.5±3.3	65.4±1.6	39.9±1.3	60.5±2.3	19.1±1.07	100.5±2.3	1.21±0.09	0.82±0.03
Sham-Exercise	445.8±12.5	3.15±0.13*	4.30±0.09*	39.9±3.9*	78.6±4.3*	41.6±2.8	54.0±1.6	18.6±1.70	115.2±4.1*	0.95±0.04	0.72±0.05
+BAT	493.5±14.5	2.85±0.12	4.29±0.15*	31.1±3.3	77.0±2.1*	41.9±2.3	57.7±1.3	20.7±1.31	112.3±2.7*	1.16±0.10	0.88±0.12

Data are mean ± S.E.M (n=6/group). Asterisks represent difference vs. Sham-Sedentary (*$P<0.05$).

Supplemental Table III. Lipokine profile Sham-Sedentary vs. +BAT.			
	fold change	**P value**	**False Discovery Rate**
Tetranor-12-HETE	0.746338	0.240576	0.45858
9-oxoODE	-1.17266	0.244575	0.45858
13-oxoODE	-1.58813	0.172033	0.4318
9-HOTrE	0.833693	0.208932	0.44503
13-HOTrE/13-HOTrE(r)	-1.87207	0.139867	0.4188
9-HODE	1.340782	0.034358*	0.28108
13-HODE	0.905538	0.191443	0.44503
9(10)-EpOME	-1.45245	0.209943	0.44503
12(13)-EpOME	1.63017	0.016309*	0.24464
9,10-diHOME	2.166779	0.00148**	0.0666
12,13-diHOME	2.147632	0.000683***	0.06147
15-deoxy-delta12,14-PGJ2	-0.30135	0.745039	0.87111
15-oxoETE	-2.51279	0.102241	0.3834
18-HEPE	-2.15289	0.055221	0.33133
15-HEPE	-1.84802	0.153561	0.4188
12-HEPE	1.331356	0.062463	0.33904
5-HEPE	0.22954	0.754964	0.87111
11-HEPE	0.925116	0.129063	0.40054
8-HEPE	-1.37195	0.229147	0.44833
9-HEPE	1.072625	0.117898	0.39568
12-oxoETE	1.117024	0.037477*	0.28108
14(15)-EpETE	0.27015	0.657054	0.85703
5-oxoETE	-2.14551	0.118705	0.39568
14(15)-EET	-2.52179	0.099651	0.3834
15-HETE	-0.20725	0.769261	0.87534
12-HETE	0.771612	0.17272	0.4318
5-HETE	-2.32542	0.112311	0.39568
20-HETE	1.714065	0.054428	0.33133
11-HETE	0.210013	0.72949	0.87111
17-HETE	0.660987	0.223723	0.44745
18-HETE	0.866479	0.101297	0.3834
9-HETE	0.803715	0.17882	0.43497
8-HETE	0.696643	0.19899	0.44503
5-HETrE	1.325602	0.212626	0.44503

8-HETrE	1.37088	0.008378**	0.24464
15-HETrE	-0.13612	0.842102	0.89164
12-oxoLTB4	-3.01622	0.085809	0.36775
PGA2/PGJ2	-0.16002	0.825793	0.88585
PGB2	0.340306	0.580272	0.81435
15-deoxy-delta12,14-PGD2	1.141287	0.027757*	0.27757
13,14-dihydro-15-keto PGA2	-0.24388	0.740336	0.87111
Bicyclo PGE2	-0.87035	0.333083	0.56221
delta12-PGJ2	-0.25811	0.735944	0.87111
LTB4	-0.15164	0.826794	0.88585
5,6-diHETE	-1.90229	0.147731	0.4188
Hepoxilin A3	-0.4368	0.588143	0.81435
17,18-diHETE	1.03871	0.06404	0.33904
PGA1	-0.38828	0.677918	0.87111
5,6-diHETrE	-1.21573	0.267578	0.48164
8,9-diHETrE	0.202183	0.750805	0.87111
11,12-diHETrE	0.491953	0.421531	0.64301
14,15-diHETrE	0.389207	0.512368	0.75595
2,3-dinor TxB2	-0.09871	0.914098	0.93594
17-HDHA	-0.46342	0.5592	0.79886
14-HDHA	0.552809	0.390752	0.61698
7-HDHA	0.353102	0.549474	0.79762
4-HDHA	-0.82893	0.355457	0.57127
8-HDHA	0.852695	0.199495	0.44503
10-HDHA	1.308327	0.082333	0.36775
11-HDHA	0.206038	0.745001	0.87111
13-HDHA	-0.07169	0.928007	0.93843
16-HDHA	-0.18864	0.787805	0.87534
20-HDHA	0.06776	0.91514	0.93594
19(20)-EpDPE	0.972918	0.085333	0.36775
16(17)-EpDPE	-0.37171	0.618412	0.82199
PGD3/PGE3	-2.13759	0.126826	0.40054
13,14-dihydro-15-keto PGE2	-0.59027	0.466985	0.70048
13,14-dihydro-15-keto PGD2	-0.83878	0.354377	0.57127
15-keto-PGF2a	-0.16169	0.814856	0.88585
PGE2/PGD2	-0.38273	0.609073	0.82199
PGD2	0.181338	0.780166	0.87534
LXA4	-0.02571	0.970212	0.97021
LXB4	-1.74088	0.16643	0.4318

PGF2a	1.400233	0.032543*	0.28108
8-iso PGF2a	1.56653	0.016178*	0.24464
5-iPF2a-VI	0.842224	0.250195	0.45954
PGE1/PGD1	0.57967	0.29853	0.52682
11-beta-PGF2a/PGF2b	1.448005	0.015767*	0.24464
13,14-dihydro-15-keto PGF2a	.	0.055221	0.33133
PD1	-1.817	0.149038	0.4188
19,20-diHDPA	-0.07156	0.914667	0.93594
TxB3	2.083207	0.027453*	0.27757
6-keto PGE1	-1.40663	0.221734	0.44745
TxB2	1.283248	0.022976*	0.27757
6-keto-PGF1a	-0.36822	0.621058	0.82199
19/20-OH PGF2a	-1.08634	0.306676	0.53079
6,15-diketo-13,14-dihydro PGF1a	-3.74189	0.07145	0.35725
RvD1	0.657904	0.416588	0.64301
PGF1a	0.560558	0.337324	0.56221
13,14-dihydro PGE1	0.219825	0.720816	0.87111

(*P<0.05; **P<0.01; ***P<0.001 vs. Sham-Sedentary).

Supplemental Table IV. Lipokine profile Sham-Sedentary vs. Sham-Exercise.			
	fold change	**P value**	**False Discovery Rate**
Tetranor-12-HETE	-0.10188	0.85862	0.93282
9-oxoODE	-0.83386	0.261571	0.57418
13-oxoODE	-0.72764	0.328123	0.64686
9-HOTrE	1.502456	0.007199**	0.16198
13-HOTrE/13-HOTrE(r)	-1.12371	0.174946	0.44934
9-HODE	1.028299	0.053567	0.35299
13-HODE	1.107356	0.04955*	0.35299
9(10)-EpOME	1.11076	0.053513	0.35299
12(13)-EpOME	1.112305	0.067617	0.35299
9,10-diHOME	1.537453	0.001878**	0.07989
12,13-diHOME	1.610793	0.000915***	0.07989
15-deoxy-delta12,14-PGJ2	-0.76385	0.387432	0.66441
15-oxoETE	-2.14479	0.060857	0.35299
18-HEPE	-0.72327	0.456435	0.70826

15-HEPE	0.081048	0.90784	0.94133
12-HEPE	0.436088	0.38565	0.66441
5-HEPE	0.493319	0.525706	0.71687
11-HEPE	0.143068	0.809682	0.92242
8-HEPE	-0.79849	0.274896	0.58906
9-HEPE	0.233836	0.631299	0.81167
12-oxoETE	0.353496	0.567534	0.74955
14(15)-EpETE	0.156006	0.790128	0.92242
5-oxoETE	-1.80195	0.081026	0.35299
14(15)-EET	-0.54511	0.406029	0.66441
15-HETE	-0.44879	0.481946	0.71687
12-HETE	0.504761	0.292248	0.59778
5-HETE	-1.04996	0.179735	0.44934
20-HETE	-0.11454	0.909952	0.94133
11-HETE	-0.57423	0.380431	0.66441
17-HETE	0.495706	0.28163	0.58946
18-HETE	0.924867	0.04522*	0.35299
9-HETE	0.342999	0.472566	0.71687
8-HETE	0.454108	0.330619	0.64686
5-HETrE	1.599462	0.002663**	0.07989
8-HETrE	0.638499	0.170639	0.44934
15-HETrE	0.046265	0.932767	0.95397
12-oxoLTB4	-2.53557	0.046628*	0.35299
PGA2/PGJ2	-1.8389	0.07725	0.35299
PGB2	-0.60843	0.435842	0.68817
15-deoxy-delta12,14-PGD2	-0.68835	0.34729	0.65117
13,14-dihydro-15-keto PGA2	-1.09276	0.192214	0.46755
Bicyclo PGE2	-1.72971	0.088128	0.35299
delta12-PGJ2	-2.18209	0.060324	0.35299
LTB4	-0.81131	0.256434	0.57418
5,6-diHETE	-1.19038	0.149562	0.42429
Hepoxilin A3	-0.59434	0.399386	0.66441
17,18-diHETE	0.478425	0.512204	0.71687
PGA1	-1.52989	0.146919	0.42429
5,6-diHETrE	-0.46034	0.574657	0.74955
8,9-diHETrE	0.243203	0.733164	0.8798
11,12-diHETrE	0.107886	0.861377	0.93282
14,15-diHETrE	0.252023	0.688811	0.8461
2,3-dinor TxB2	-0.82158	0.39866	0.66441

17-HDHA	-2.17546	0.063726	0.35299
14-HDHA	0.077762	0.880997	0.93282
7-HDHA	-1.50983	0.150857	0.42429
4-HDHA	-1.72495	0.100655	0.36544
8-HDHA	-0.0433	0.958732	0.96583
10-HDHA	0.337663	0.487813	0.71687
11-HDHA	-0.02297	0.965825	0.96583
13-HDHA	-0.22742	0.695682	0.8461
16-HDHA	0.174761	0.754284	0.89323
20-HDHA	-0.15189	0.829791	0.93282
19(20)-EpDPE	0.76316	0.102611	0.36544
16(17)-EpDPE	-0.26133	0.656385	0.83204
PGD3/PGE3	-2.48934	0.055078	0.35299
13,14-dihydro-15-keto PGE2	-1.70646	0.086657	0.35299
13,14-dihydro-15-keto PGD2	-1.73327	0.090208	0.35299
15-keto-PGF2a	-0.83845	0.261478	0.57418
PGE2/PGD2	-1.44602	0.111553	0.36544
PGD2	-2.03888	0.069933	0.35299
LXA4	-1.48823	0.113691	0.36544
LXB4	-0.51568	0.419927	0.67488
PGF2a	-0.53644	0.405108	0.66441
8-iso PGF2a	-0.40091	0.513415	0.71687
5-iPF2a-VI	0.460374	0.346435	0.65117
PGE1/PGD1	-1.16796	0.178035	0.44934
11-beta-PGF2a/PGF2b	-0.41401	0.501678	0.71687
13,14-dihydro-15-keto PGF2a	-1.55696	0.107029	0.36544
PD1	-2.83357	0.040073*	0.35299
19,20-diHDPA	-0.42274	0.554635	0.74503
TxB3	-0.1006	0.876469	0.93282
6-keto PGE1	-2.25626	0.058617	0.35299
TxB2	-0.09297	0.867369	0.93282
6-keto-PGF1a	-1.70406	0.088535	0.35299
19/20-OH PGF2a	0.617815	0.252181	0.57418
6,15-diketo-13,14-dihydro PGF1a	-1.47151	0.126195	0.39164
RvD1	-0.42469	0.521566	0.71687
PGF1a	0.21776	0.669666	0.83708
13,14-dihydro PGE1	-0.1426	0.806903	0.92242

(*$P<0.05$; **$P<0.01$; ***$P<0.001$ vs. Sham-Sedentary).

Supplemental Table V. Echocardiography parameters.

	Heart Rate	Diameter (Systole)	Diameter (Diastole)	Volume (Systole)	Volume (Diastole)	Stroke Volume	Ejection Fraction	Cardiac Output	LV Mass	LVPW (Systole)	LVPW (Diastole)
Baseline	409.5±18.4	2.74±0.10	3.9±0.12	28.4±2.5	66.7±4.6	38.3±2.9	57.5±2.0	15.6±1.33	111.9±8.0	1.10±0.05	0.76±0.04
Sham	438.8±12.9	3.11±0.09	4.07±0.05	38.6±2.8	73.0±2.3	34.4±2.0	44.2±2.7**	15.0±0.65	149.9±10.8*	1.07±0.10*	0.95±0.08
TNT-Ephx1/2	491.7±21.3*	2.97±0.11	4.13±0.13	34.7±3.0	76.1±5.8	41.3±4.0	52.1±2.7	20.4±2.13	121.8±8.8	1.07±0.05	0.78±0.03
TNT-Ucp1	458.2±16.4	3.31±0.19*	4.41±0.16*	45.3±6.1*	89.0±7.5*	43.7±2.1	47.4±2.8*	20.0±1.29	146.1±4.5*	0.97±0.08	0.78±0.04

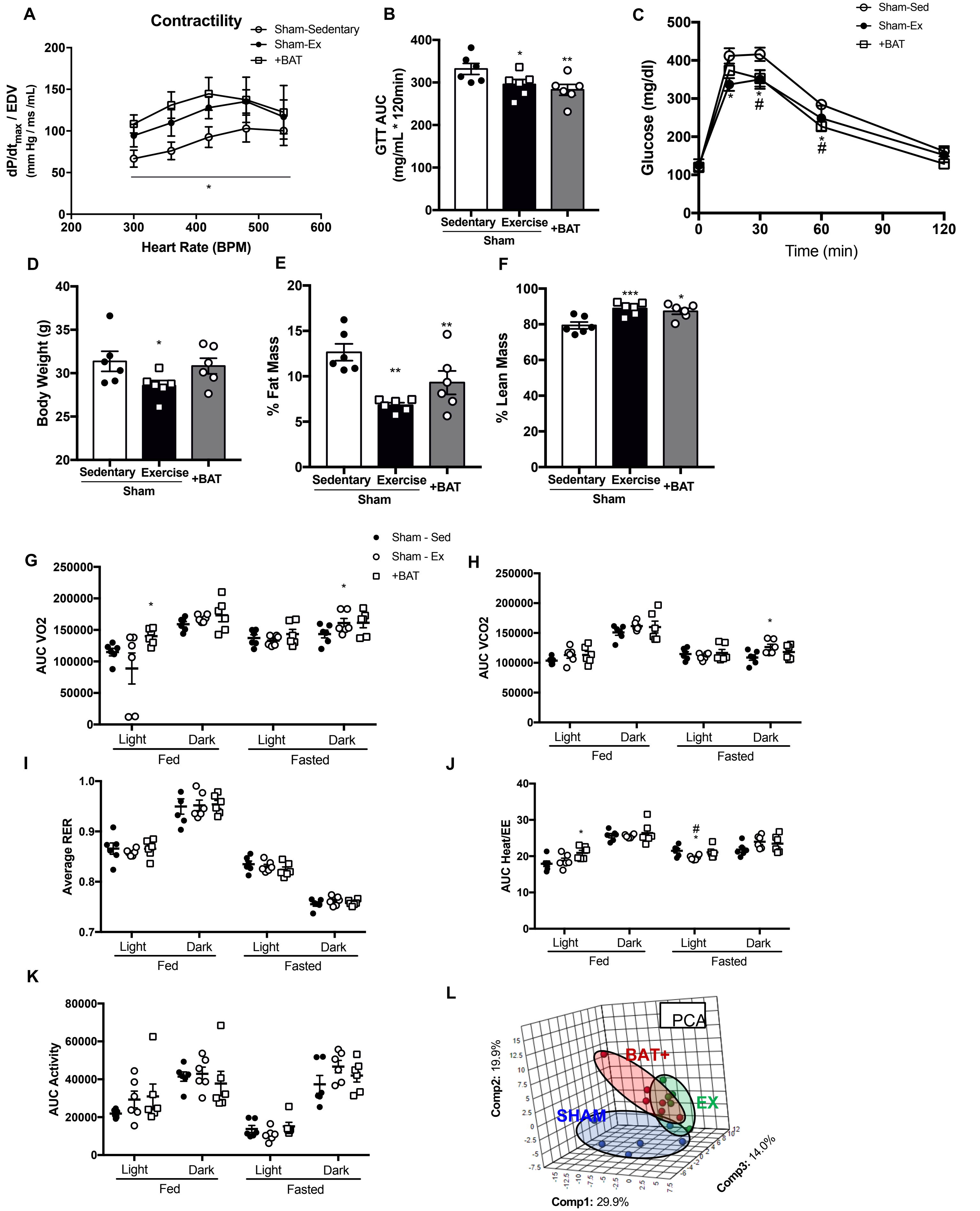
Data are mean ± S.E.M. Baseline (n=8), Sham (n=5), TNT-Ephx1/2 (n=7), or TNT-Ucp1 (n=5). Data are mean ± S.E.M Asterisks represent differences compared to baseline cohort (**P*<0.05; ***P*<0.01).

Supplemental Table VI. Human subject characteristics.

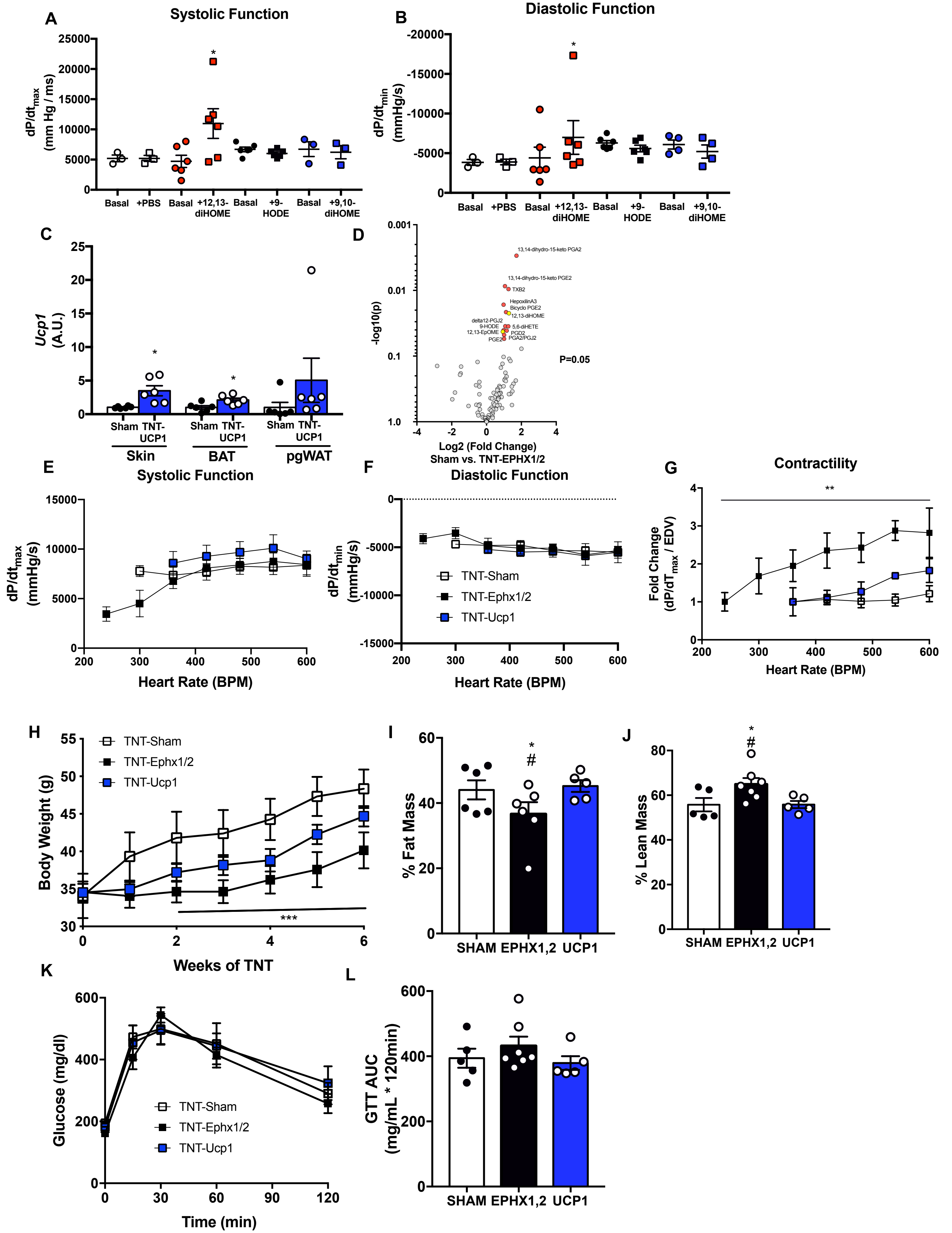
	Healthy	**Heart Disease**
Sex no.		
Male	25	17
Female	26	7
Age (years)		
Male	56.3 ± 4.4	65.4 ± 2.4
Female	43.2 ± 3.1$^{\$}$	62.4 ± 7.4
BMI (kg/m^2)		
Male	24.8 ± 1.1	26.5 ± 2.7
Female	23.4 ± 0.4	26.1 ± 1.9
Glucose (mg/dL)		
Male	93.1 ± 2.5	137.1 ± 12.2*
Female	90.5 ± 3.9	97.1 ± 4.2

Data are Mean ± SEM. **P*<0.05 heart disease males vs. healthy males; $^{\$}$*P*<0.05 healthy females vs. healthy males.

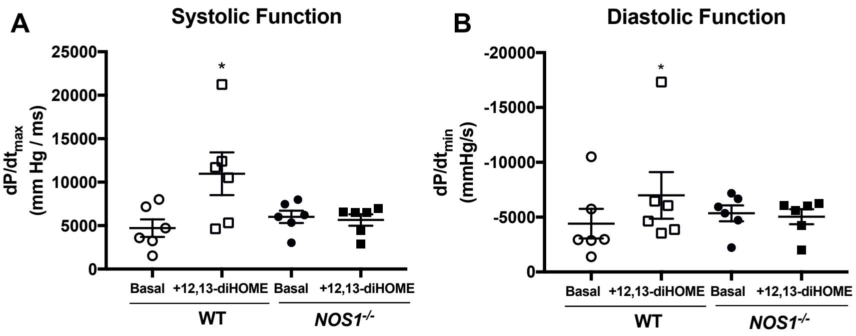
Supplemental Figure I



Supplemental Figure II



Supplemental Figure III



Supplemental Figures Legends.

Supplemental Figure I. Exercise and +BAT have similar effects on metabolic health. (A) Contractility (dp/dt max normalized by EDV), (B) glucose tolerance test area under the curve (GTT AUC), (C) glucose excursion curve, (D) body weight, (E) % fat mass, (F) % lean mass, (G) Vo_2, (H) Vco_2, (I) RER, (J) Heat/energy expenditure, and (K) activity in Sham-Sedentary, Sham-Exercised, or +BAT mice 12 wks after transplantation (8 wks of exercise). Data are mean $\pm$ S.E.M (n=6/group). Asterisks represent difference vs. Sham-Sedentary (**P*<0.05; ***P*<0.01; ****P*<0.001). (L) Principal component analysis (PCA) of serum oxylipins from Shem-Sedentary, Sham-Exercised, or +BAT mice 12 wks after transplantation (8 wks of exercise). One-way ANOVA was used for **B, D, E, F, G, H, I,** and **J** with Tukey's multiple comparisons tests. Two-way ANOVA was used for **A** and **C** with Tukey's multiple comparisons tests.

Supplemental Figure II. Effects of sustained treatment with 12,13-diHOME (TNT) metabolism and cardiac function. (A) Systolic and (B) diastolic function in mice acutely injected with saline (n=3), 12,13-diHOME (n=8), 9-HODE (n=5), or 9,10-diHOME (n=3). Data are mean $\pm$ S.E.M. Asterisks represent difference compared to all other groups (**P*<0.05; ***P*<0.01). (C) Gene expression data of *Ucp1* in skin, BAT, and pgWAT of Sham and TNT-Ucp1 mice. Data are mean $\pm$ S.E.M Asterisks represent difference compared to all other groups (**P*<0.05). (D) Volcano plot representing 88 lipids comparing the fold induction of Sham and TNT-Ephx1/2 mice to the p value. (E) Systolic function and (F) diastolic function measured by *in vivo* cardiac hemodynamics. Data are mean $\pm$ S.E.M (n=5-7/group). (G) Contractility (dp/dt max normalized per EDV) Data are mean $\pm$ S.E.M (n=5-7/group). (H) Body weight, (I) % fat mass, and (J) % lean mass after 6 wks of TNT. (K) GTT AUC, and (L) glucose excursion curve after 6 wks of TNT. Asterisks represent difference compared to Sham (**P*<0.05; ***P*<0.01; ***P<0.001); # represent differences compared to TNT-Ucp1(#*P*<0.05). Paired two-tailed Student's t-test was used for **A** and **B**. Unpaired two-tailed Student's t-test was used for **C**. Two-way ANOVA was used for **E, F, G, H,** and **K** with Tukey's multiple comparisons tests. One-way ANOVA was used for **I, J,** and **L** with Tukey's multiple comparisons tests.

Supplemental Figure III. Effects of acute treatment with 12,13-diHOME on cardiac function in *NOS1$^{-/-}$* mice. (A) Systolic and (B) diastolic function in WT mice (n=6) or *NOS1$^{-/-}$* mice (n=6) acutely injected with 12,13-diHOME. Data are mean $\pm$ S.E.M. Asterisks represent difference compared to pre-injection values (**P*<0.05). Paired two-tailed Student's t-test was used for **A** and **B**.

Supplementary Video 1

Representative imaging of FFA-SS-Luc uptake in cardiomyocytes isolated from *LucTg* mice and treated with 12,13-diHOME or vehicle and then incubate with luciferin-conjugated fatty acid. Data from individual images using sequential 3 min exposures over approximately 30 minutes was stacked into a movie. The wells on the left are vehicle treated, while the wells on the right are treated with 12,13-diHOME.