Inventory of Supplemental Information

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Supplemental Table 1. Related to Figure 1.

Signaling Lipids in Humans Pre- vs. Post-Exercise					
Lipid	**Avg Pre-Exercise**	**SEM**	**Avg Post-Exercise**	**SEM**	**p-value**
IS-d4-9,10-diHOME	0.0000	0.0000	0.0000	0.0000	0.0000
Tetranor-12-HETE	0.0473	0.0071	0.0323	0.0035	0.0646
9-oxoODE	0.1293	0.0166	0.0790	0.0094	0.0117
13-oxoODE	0.4271	0.0442	0.2706	0.0411	0.0122
9-HOTrE	0.1101	0.0158	0.0691	0.0110	0.0379
13-HOTrE/13-HOTrE(r)	0.0531	0.0053	0.0357	0.0042	0.0131
9-HODE	1.4517	0.2541	1.3389	0.1472	0.7026
13-HODE	2.0219	0.2422	1.2251	0.1141	0.0049
9(10)-EpOME	3.8920	0.5678	2.1015	0.2415	0.0062
12(13)-EpOME	1.4799	0.2207	1.8134	0.1773	0.2442
9,10-diHOME	1.3140	0.2840	1.9588	0.4610	0.2397
12,13-diHOME*	1.2308	0.1774	2.5021	0.3343	0.0017
15-deoxy-delta12,14-PGJ2	0.0148	0.0033	0.0126	0.0016	0.6048
15-oxoETE	0.0941	0.0146	0.0652	0.0134	0.1494
18-HEPE	0.0132	0.0021	0.0114	0.0016	0.5482
15-HEPE	0.0121	0.0023	0.0108	0.0015	0.6982
12-HEPE	0.0190	0.0030	0.0229	0.0037	0.4653
5-HEPE	0.0215	0.0036	0.0147	0.0022	0.1483
11-HEPE	0.0110	0.0019	0.0087	0.0010	0.3565
8-HEPE	0.0142	0.0036	0.0093	0.0016	0.4145
9-HEPE	0.0108	0.0008	0.0069	0.0007	0.0030
12-oxoETE	0.0132	0.0015	0.0077	0.0013	0.0302
14(15)-EpETE	0.0089	0.0010	0.0072	0.0008	0.3102
17(18)-EpETE	0.0078	0.0009	0.0075	0.0012	0.9092
5-oxoETE	0.0125	0.0016	0.0113	0.0015	0.6210
14(15)-EET	0.0413	0.0050	0.0260	0.0033	0.0140
11(12)-EET	0.0061	0.0010	0.0048	0.0005	0.3917
8(9)-EET	0.0065	0.0006	0.0053	0.0005	0.5482
5(6)-EET	0.0000	0.0000	0.0027	0.0003	0.0000
15-HETE	0.0360	0.0037	0.0310	0.0040	0.3591
12-HETE	0.7583	0.2222	1.4780	0.5768	0.2519
5-HETE	0.1152	0.0133	0.1067	0.0113	0.6270
20-HETE	0.0280	0.0044	0.0230	0.0028	0.3415
11-HETE	0.1799	0.0245	0.1816	0.0347	0.9693
16-HETE	0.0198	0.0048	0.0164	0.0044	0.6330
17-HETE	0.0305	0.0036	0.0292	0.0040	0.8132
18-HETE	0.0463	0.0051	0.0429	0.0054	0.6481
9-HETE	0.0289	0.0069	0.0328	0.0086	0.7265
8-HETE	0.0257	0.0042	0.0241	0.0033	0.7652

5-HETrE	0.0175	0.0029	0.0151	0.0017	0.5125
8-HETrE	0.0159	0.0022	0.0197	0.0039	0.4322
15-HETrE	148.2692	10.5400	130.7339	10.0428	0.2335
2,3-dinor-11beta-PGF2a	0.0060	0.0004	0.0040	0.0003	0.0678
tetranor-PGFM	0.0048	0.0004	0.0073	0.0007	0.2945
12-oxoLTB4	0.0108	0.0014	0.0049	0.0004	0.0112
PGA2/PGJ2	0.0073	0.0010	0.0056	0.0006	0.2730
PGB2	0.0075	0.0010	0.0093	0.0017	0.6495
15-deoxy-delta12,14-PGD2	0.0086	0.0010	0.0057	0.0006	0.1730
13,14-dihydro-15-keto PGA2	0.0100	0.0018	0.0128	0.0031	0.5429
Bicyclo PGE2	0.0075	0.0011	0.0058	0.0007	0.2913
delta12-PGJ2	0.0072	0.0010	0.0066	0.0010	0.7760
LTB4	0.0158	0.0033	0.0165	0.0023	0.8642
5,6-diHETE	0.0183	0.0043	0.0366	0.0113	0.1480
5,15-diHETE	0.0048	0.0006	0.0062	0.0007	0.3230
Hepoxilin A3	0.0100	0.0014	0.0087	0.0007	0.4798
14,15-diHETE	0.0102	0.0013	0.0068	0.0011	0.1785
17,18-diHETE	0.1301	0.0206	0.1379	0.0129	0.7505
PGA1	0.0067	0.0005	0.0068	0.0011	0.9256
5,6-diHETrE	0.0147	0.0031	0.0177	0.0021	0.4621
8,9-diHETrE	0.0306	0.0043	0.0280	0.0044	0.6653
11,12-diHETrE	0.1568	0.0159	0.1290	0.0106	0.1526
14,15-diHETrE	0.1561	0.0193	0.1517	0.0106	0.8433
2,3-dinor TxB2	0.0062	0.0006	0.0065	0.0006	0.7845
17-HDHA	0.8257	0.7073	0.2912	0.2441	0.5392
14-HDHA	0.0065	0.0011	0.0120	0.0019	0.0516
7-HDHA	0.0064	0.0011	0.0060	0.0009	0.8200
4-HDHA	0.0153	0.0026	0.0100	0.0020	0.1535
8-HDHA	0.0116	0.0015	0.0062	0.0006	0.0357
10-HDHA	0.0147	0.0024	0.0114	0.0015	0.3046
11-HDHA	0.0119	0.0014	0.0115	0.0016	0.8833
13-HDHA	0.0113	0.0021	0.0062	0.0008	0.1057
16-HDHA	0.0113	0.0021	0.0102	0.0014	0.6820
20-HDHA	0.0106	0.0016	0.0101	0.0020	0.8686
19(20)-EpDPE	0.0168	0.0021	0.0096	0.0017	0.0180
16(17)-EpDPE	0.0120	0.0015	0.0122	0.0021	0.9410
PGD3/PGE3	0.0083	0.0011	0.0070	0.0010	0.5712
15-keto-PGE2	0.0000	0.0000	0.0084	0.0000	0.0000
PGK2	0.0060	0.0010	0.0065	0.0010	0.8381
13,14-dihydro-15-keto PGE2	0.0075	0.0012	0.0093	0.0009	0.3801
13,14-dihydro-15-keto PGD2	0.0072	0.0012	0.0060	0.0006	0.5040
15-keto-PGF2a	0.0076	0.0013	0.0057	0.0006	0.4163

PGE2/PGD2	0.0105	0.0016	0.0140	0.0020	0.2343
PGD2	0.0083	0.0012	0.0063	0.0005	0.2691
LXA4	0.0082	0.0014	0.0063	0.0010	0.3910
LXB4	0.0062	0.0011	0.0073	0.0011	0.6203
PGF2a	0.0095	0.0013	0.0126	0.0017	0.2042
8-iso PGF2a	0.0099	0.0013	0.0117	0.0015	0.4320
5-iPF2a-VI	0.0241	0.0094	0.0149	0.0016	0.3548
PGE1/PGD1	0.0076	0.0009	0.0075	0.0008	0.9684
11-beta-PGF2a/PGF2b	0.0101	0.0013	0.0114	0.0015	0.5718
13,14-dihydro-15-keto PGF2a	0.0106	0.0011	0.0124	0.0017	0.4132
Maresin1	0.0000	0.0000	0.0036	0.0003	0.0000
PD1	0.0086	0.0011	0.0074	0.0013	0.6604
19,20-diHDPA	0.0845	0.0130	0.0843	0.0084	0.9927
20-carboxy LTB4	0.0319	0.0085	0.0133	0.0023	0.1036
TxB3	0.0088	0.0011	0.0146	0.0037	0.2241
11-dehydro TxB2	0.0069	0.0014	0.0052	0.0006	0.4553
19/20-OH PGE2	0.0065	0.0006	0.0059	0.0004	0.7715
6-keto PGE1	0.0043	0.0005	0.0059	0.0006	0.2995
TxB2	1.9404	0.7048	3.0967	1.4077	0.4668
6-keto-PGF1a	0.0171	0.0032	0.0208	0.0058	0.6258
19/20-OH PGF2a	0.0079	0.0009	0.0059	0.0005	0.2707
6,15-diketo-13,14-dihydro PGF1a	0.0077	0.0010	0.0057	0.0004	0.2658
RvD1	0.0064	0.0006	0.0043	0.0004	0.1566
RvD2	0.0061	0.0011	0.0080	0.0017	0.6787
LTE4	0.0127	0.0018	0.0009	0.0000	0.0000
LTD4	0.0060	0.0013	0.0062	0.0007	0.9620
LTC4	0.0082	0.0001	0.0048	0.0004	0.0429
d4-9-HODE	0.0000	0.0000	0.0000	0.0000	0.0000
d8-5S-HETE	0.0000	0.0000	0.0000	0.0000	0.0000
d4-LTB4	0.0000	0.0000	0.0000	0.0000	0.0000
d4-PGE2	0.0000	0.0000	0.0000	0.0000	0.0000
PGF1a	0.0943	0.0082	0.0943	0.0079	0.9993
13,14-dihydro PGE1	0.0422	0.0066	0.0348	0.0047	0.4164

Supplemental Table 2. Related to Figure 1.

% Fat Mass as a Covariate
Spearman correlation coefficient

Variable correlated with 12 13 diHOME	R	P
VO2peak (ml/Kg/min)	0.1214	0.4679
Body Mass Index (kg/m^2)	-0.2877	0.0647
Triglycerides (mg/dL)	-0.3554	0.0209
Weight Average (kg)	-0.2433	0.1410

Pearson correlation coefficient

Variable correlated with 12 13 diHOME	R	P
VO2peak (ml/Kg/min)	0.1889	0.2560
Body Mass Index (kg/m^2)	-0.2968	0.0563
Triglycerides (mg/dL)	-0.3827	0.0124
Weight Average (kg)	-0.2403	0.1462

Supplemental Table 3. Related to Figure 2.

Signaling Lipids in BAT (Sedentary vs. Trained)					
Lipid	**Avg Sed**	**SEM**	**Avg Train**	**SEM**	**p-value**
9-oxoODE	2.710	0.623	2.828	0.728	0.904
13-oxoODE	1.629	0.282	2.739	0.885	0.277
9-HOTrE	0.364	0.089	0.496	0.167	0.505
HOTrE/13-HOTrE	0.269	0.059	0.375	0.086	0.338
9-HODE	13.241	2.444	17.024	5.984	0.578
13-HODE	20.447	3.203	23.406	8.180	0.747
9(10)-EpOME	13.643	1.763	17.130	3.027	0.349
12(13)-EpOME	10.681	1.586	12.628	2.859	0.568
9,10-diHOME	3.471	0.381	5.366	1.055	0.140
12,13-diHOME*	**2.704**	**0.317**	**4.703**	**0.738**	**0.0427**
18-HEPE	0.143	0.021	0.170	0.029	0.467
15-HEPE	0.093	0.010	0.115	0.027	0.481
12-HEPE	1.637	0.238	1.798	0.655	0.825
5-HEPE	0.189	0.026	0.241	0.048	0.368
11-HEPE	0.107	0.013	0.140	0.027	0.316
8-HEPE	0.062	0.008	0.083	0.024	0.422
15-oxoETE	0.059	0.016	0.055	0.010	0.847
9-HEPE	0.038	0.007	0.054	0.019	0.457
14(15)-EET	0.274	0.054	0.286	0.051	0.873
11(12)-EET	0.415	0.069	0.489	0.127	0.626
8(9)-EET	0.057	0.028	0.071	0.033	0.758
5(6)-EET	0.100	0.014	0.102	0.026	0.941
15-HETE	0.406	0.056	0.468	0.110	0.632
12-HETE	3.721	1.100	2.277	0.772	0.311
5-HETE	0.629	0.111	0.569	0.091	0.682
20-HETE	0.007	0.003	0.011	0.004	0.476
11-HETE	0.889	0.110	0.947	0.188	0.797
16-HETE	0.007	0.007	0.021	0.013	0.332
17-HETE	0.014	0.004	0.024	0.008	0.273
18-HETE	0.091	0.008	0.123	0.028	0.311
9-HETE	0.216	0.044	0.151	0.038	0.291
8-HETE	0.256	0.040	0.246	0.062	0.892
all trans-LTB4	0.013	0.007	0.003	0.002	0.235
LTB4	0.018	0.006	0.006	0.003	0.096
5,6-diHETE	0.018	0.008	0.021	0.010	0.802
5,15-diHETE	0.001	0.001	0.001	0.000	0.973
Hepoxilin A3	0.029	0.013	0.038	0.015	0.686
17-HDHA	0.078	0.009	0.113	0.030	0.317
14-HDHA	0.431	0.086	0.477	0.132	0.777
7-HDHA	0.055	0.010	0.052	0.009	0.775
4-HDHA	0.200	0.030	0.268	0.048	0.264
8-HDHA #	**0.101**	**0.039**	**0.000**	**0.000**	**0.049**
10-HDHA	0.282	0.080	0.324	0.049	0.664
11-HDHA	0.122	0.014	0.131	0.026	0.778
13-HDHA	0.242	0.038	0.292	0.064	0.525
16-HDHA	0.281	0.037	0.321	0.050	0.537
20-HDHA	0.237	0.043	0.283	0.058	0.539
19(20)-EpDPE	0.054	0.034	0.025	0.016	0.467
16(17)-EpDPE	0.168	0.030	0.147	0.042	0.692

PGE2/PGD2	0.089	0.026	0.056	0.013	0.302
PGD2	0.038	0.005	0.025	0.005	0.084
LXA4	0.028	0.011	0.033	0.006	0.726
LXB4	0.006	0.003	0.005	0.002	0.942
15-keto-PGF2a	0.007	0.002	0.006	0.002	0.794
dihydro-15-keto	0.028	0.011	0.014	0.006	0.314
dihydro-15-keto	0.020	0.005	0.027	0.008	0.493
PGF2a	0.031	0.009	0.018	0.002	0.217
PGE1/D1	0.017	0.005	0.021	0.006	0.637
8-iso PGF2a	0.030	0.009	0.020	0.003	0.336
5-iPF2a-VI	0.008	0.003	0.004	0.001	0.302
PD1	0.061	0.042	0.023	0.008	0.410
TxB2	0.029	0.008	0.017	0.006	0.224
6-keto-PGF1a	0.018	0.012	0.003	0.002	0.245
19/20-OH PGF2a	0.002	0.001	0.002	0.001	0.915
RvD1	0.003	0.001	0.005	0.002	0.565
RvD2	0.002	0.001	0.002	0.001	0.940
LTE4	0.000	0.000	0.000	0.000	N/A
LTD4	0.002	0.001	0.001	0.000	0.504
LTC4	0.001	0.000	0.000	0.000	0.094
PGF1a	0.000	0.000	0.001	0.001	0.363
PGD3	0.010	0.004	0.006	0.002	0.494
PGA2/PGJ2	0.012	0.008	0.003	0.001	0.293
PGB2	0.003	0.002	0.001	0.001	0.545
eoxy-delta12,14-P	0.007	0.002	0.007	0.003	0.977
5,6-DiHETrE #	**0.031**	**0.007**	**0.013**	**0.003**	**0.050**
8,9-DiHETrE #	**0.067**	**0.010**	**0.025**	**0.004**	**0.008**
11,12-DiHETrE	0.101	0.021	0.070	0.017	0.268
14,15-DiHETrE	0.174	0.031	0.118	0.016	0.144
5-HETrE	0.019	0.005	0.036	0.015	0.341
8-HETrE	0.172	0.020	0.137	0.032	0.374
15-HETrE	0.485	0.045	0.491	0.088	0.957
19,20-DiHDPA	0.210	0.027	0.238	0.040	0.577
dinor-11beta-PG	0.001	0.001	0.001	0.000	0.746
eoxy-delta12,14	0.011	0.005	0.009	0.004	0.868
TxB3	0.004	0.002	0.004	0.001	0.843
Tetranor-12-HETE	0.008	0.002	0.006	0.002	0.560

Supplemental Table 4. Related to Figure 2, Figure S2. Primer Sequences.

Primer	Sequence
Ephx1 F	GGAGACCTTACCACTTGAAGATG
Ephx1 R	GCCCGGAACCTATCTATCCTCT
Ephx2 F	ACCACTCATGGATGAAAGCTACA
Ephx2 R	TCAGGTAGATTGGCTCCACAG
Ephx3 F	CAGTGGACTCCGATAGCACG
Ephx3 R	TGGGACGACTACAGAGCCG
Ephx4 F	TCCCTGGTGTACGGCTACTG
Ephx4 R	ATCTTAACCCGGAGTCCTTGA
GAPDH F	AACTTTGGCATTGTGGAAGG
GAPDH R	ACACATTGGGGGTAGGAACA
Cs F	GACTACATCTGGAACACACTCAATTCA
Cs R	CGAGGGTCAGTCTTCCTCAGTAC
Nrf1 F	CAACAGGGAAGAAACGGAAA
Nrf1 R	GCACCACATTCTCCAAAGGT
Nrf2 F	AGGTTGCCCACATTCCCAAACAAG
Nrf2 R	TTGCTCCATGTCCTGCTCTATGCT
Tfam F	GTCCATAGGCACCGTATTGC
Tfam R	CCCATGCTGGAAAAACACTT
Pgc1a F	GAATCAAGCCACTACAGACACCG
Pgc1a R	CATCCCTCTTGAGCCTTTCGTG
Cd36 F	TGGAGCTGTTATTGGTGCAG
Cd36 R	TGGGTTTTGCACATCAAAGA
Fatp1 F	TGCCACAGATCGGCGAGTTCTA
Fatp1 R	AGTGGCTCCATCGTGTCCTCAT
Fatp4 F	GACTTCTCCAGCCGTTTCCACA
Fatp4 R	CAAAGGACAGGATGCGGCTATTG

Supplemental Video 1, Related to Figure 3.

Representative imaging of FFA-SS-Luc uptake in Acta1cre+/−Rosa(stop)Luc+/− injected intravenously with luciferin-conjugated fatty acid and 12,13-diHOME or vehicle. Data from individual images using sequential, thirty second exposures over approximately 15 minutes was stacked into a movie. The animal on the right is the vehicle treated and the mouse on the left is treated with 12,13-diHOME.

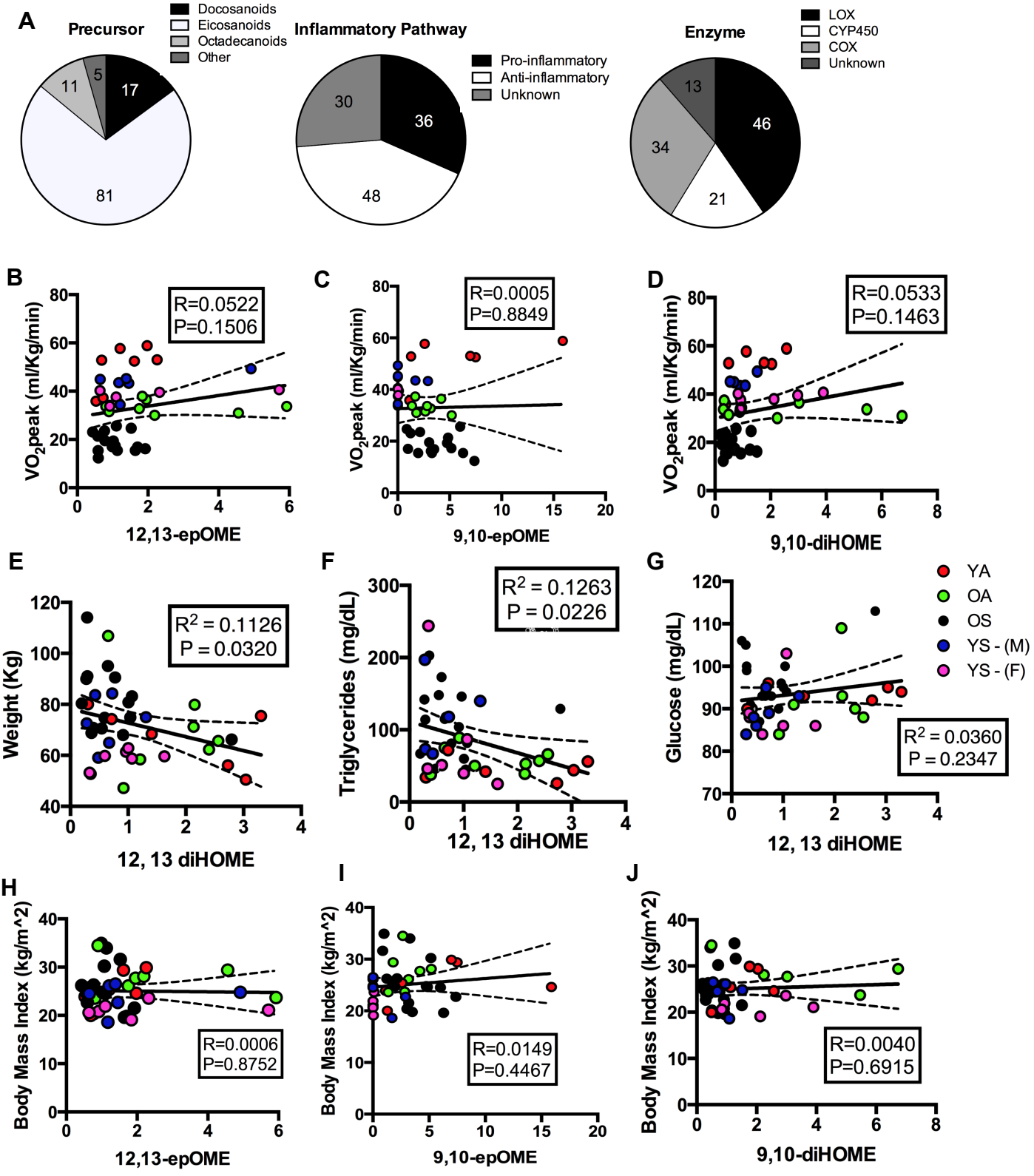
Supplemental Figure Legends.

Supplemental Figure 1. Lipidomics in human subjects after acute exercise, correlations with metabolic markers and Vo_{2peak}, related to Figure 1. (A) For all lipid species measured by LC-MS annotation of the precursor lipid species, whether the lipid was pro- or anti-inflammatory, and the enzyme pathway involved in biosynthesis of the lipid biosynthesis. (B-D) Correlations between linoleic acid metabolites (B) 12,13-epOME (n=39), (C) 9,10-epOME (n=39), and (D) 9,10-diHOME (n=39) and VO_{2peak}. (E-G) Correlations between 12,13-diHOME and all subjects (E) body weight (n=39), (F) triglycerides (n=39), and (G) glucose (n=39). Correlations between linoleic acid metabolites (H) 12,13-epOME (n=39), (I) 9,10-epOME (n=39), and (J) 9,10-diHOME (n=39) and BMI. Red (Young Active-YA, n=6), green (Older Active-OA, n=7), and black (Older Sedentary-OS, n=14) circles represent Cohort 1, while the blue (Young Sedentary Males - YS-M, n=6) and pink (Young Sedentary Females - YS-F, n=6) represent Cohort 2.

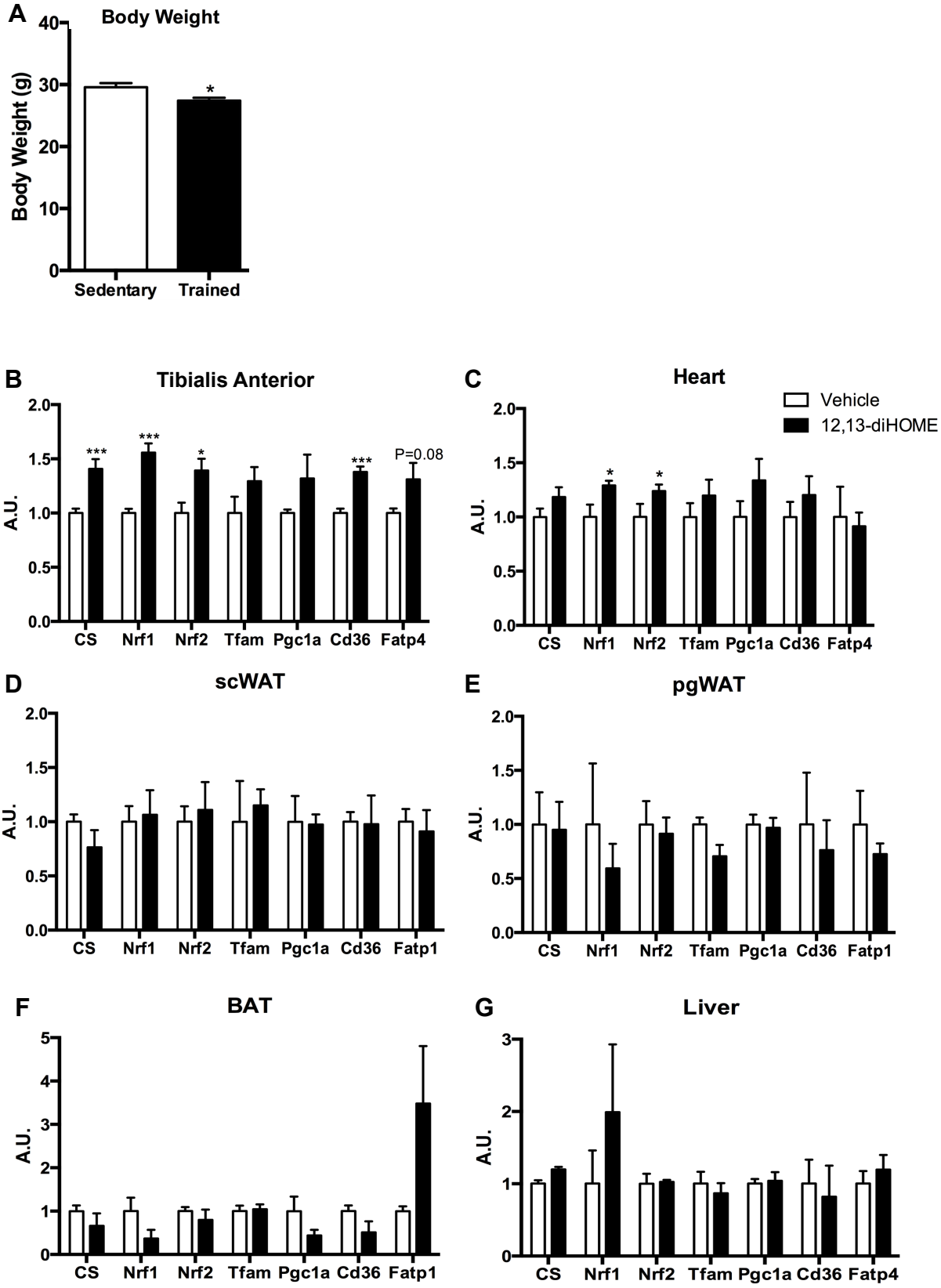
Supplemental Figure 2. Body mass after exercise; gene expression after acute injection of 12,13-diHOME, related to Figures 2 and 4. (A) Body mass in mice after 3 wks of exercise training. Data are means ± s.e.m. (n=6). Asterisks represent differences compared to pre exercise (**P*<0.05). Expression of mitochondrial and fatty acid genes in (B) tibialis anterior (TA) skeletal muscle, (C) heart, (D) subcutaneous white adipose tissue (scWAT), (E) perigonadal white adipose tissue (pgWAT), (F) brown adipose tissue (BAT), and (G) liver. Data are means ± s.e.m. (n=4/group). Asterisks represent differences compared to pre exercise (**P*<0.05; ****P*<0.001).

Supplemental Figure 3. 12,13-diHOME does not affect glucose uptake into skeletal muscle, related to Figure 4. (A) ^{3}H-2DG glucose uptake measured in differentiated C2C12 cells incubated with either vehicle or 12,13-diHOME. Data are means ± s.e.m. (n=6/group). ^{3}H-2DG Glucose uptake in isolated (B) soleus or (C) extensor digitorum longus (EDL) incubated with either vehicle or 12,13-diHOME (300 ng/ml) for one hour. Data are means ± s.e.m. (n=6/group).

Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3