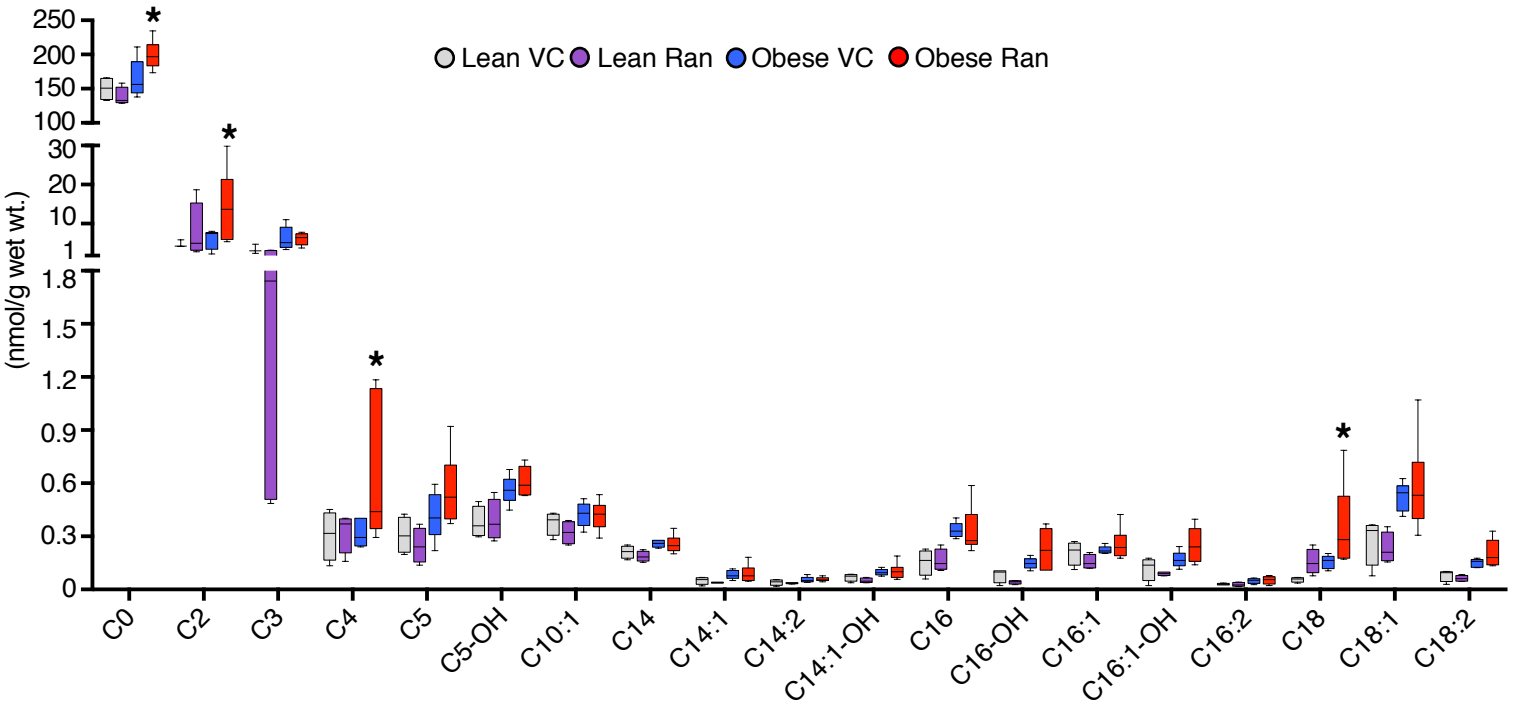
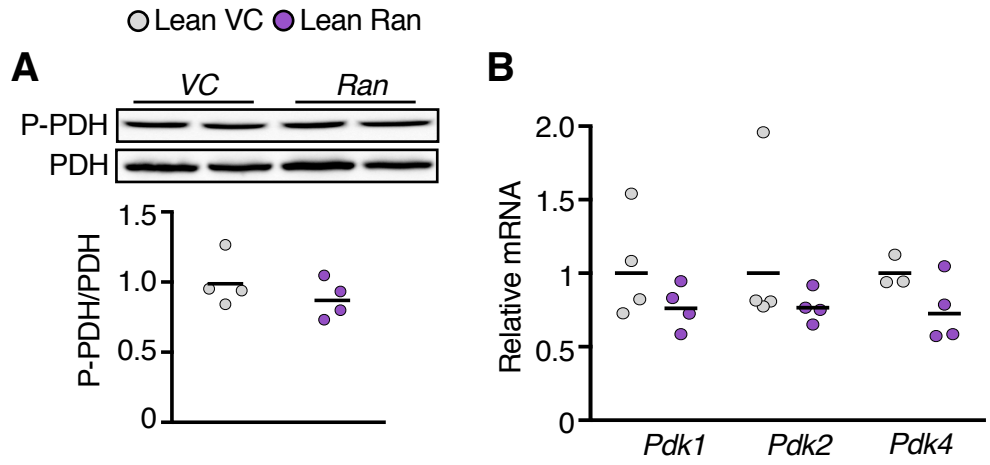
Supplemental Figure 1



Supplemental Figure 1. Hepatic acylcarnitine levels in lean and obese mice.
Acylcarnitine levels in liver samples harvested from lean and obese mice treated with either vehicle control (VC) or ranolazine (Ran) (n = 4 – 6). Values represent means ± SEM. Differences were determined using a two-way ANOVA, followed by a Bonferroni post-hoc analysis. *$P < 0.05$, Significantly different from VC counterpart.

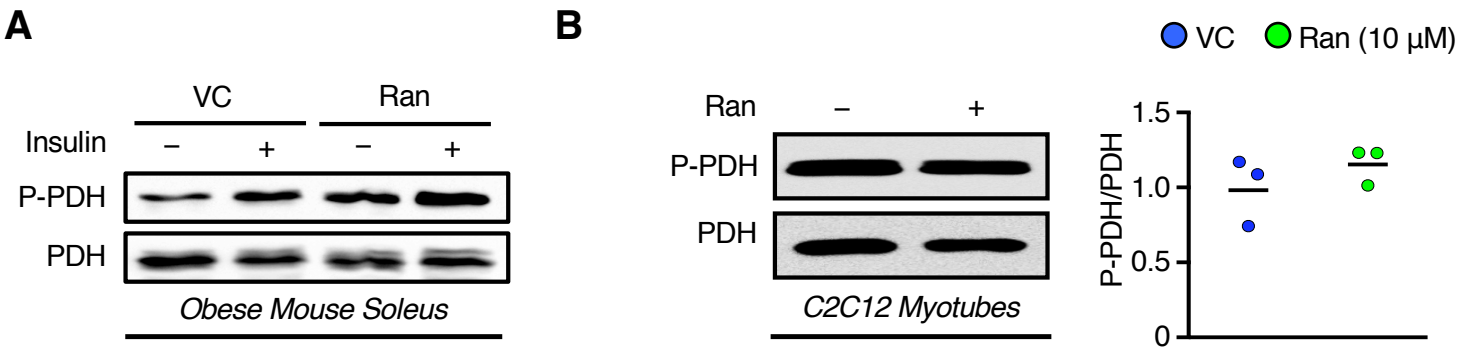
Supplemental Figure 2



Supplemental Figure 2. Ranolazine treatment does not affect PDH phosphorylation and *Pdk* mRNA expression in lean mice.

(**A**) PDH phosphorylation was evaluated by Western blot analysis in livers from lean mice treated with either vehicle control (VC) or ranolazine (Ran). (n = 6). (**B**) *Pdk* mRNA expression was measured via real-time PCR in liver RNA extracts from lean mice treated with either VC or ran (n = 4-5). Values represent mean ± SEM.

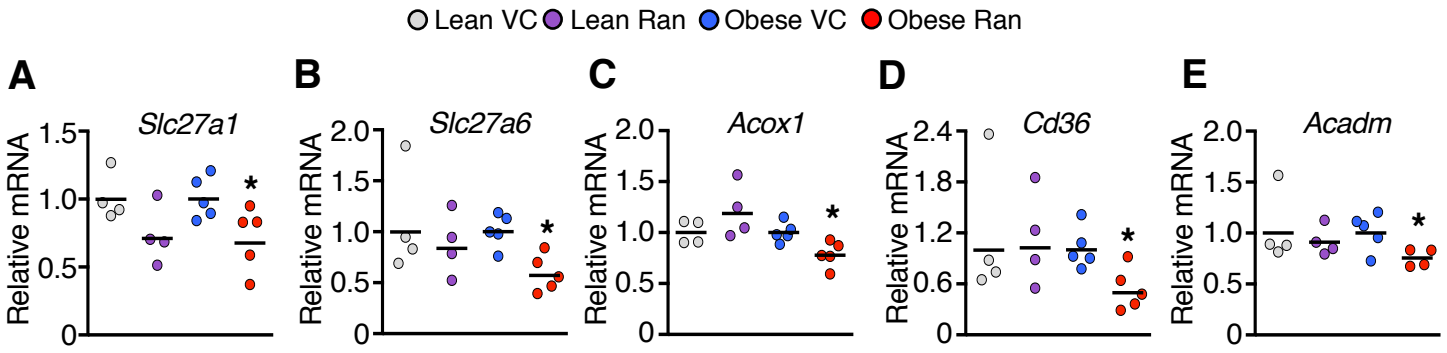
Supplemental Figure 3



Supplemental Figure 3. Ranolazine treatment does not affect PDH phosphorylation in skeletal muscle or C2C12 myotubes.

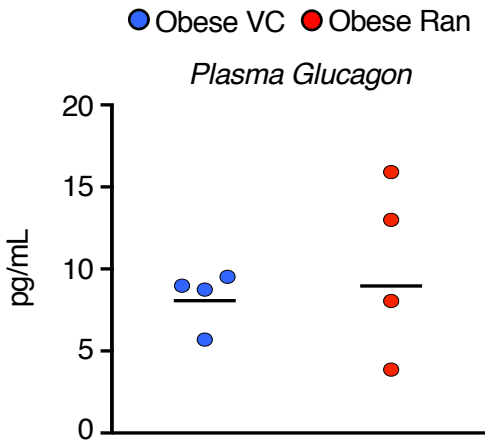
(**A**) PDH phosphorylation and PDH from soleus obese mice treated either with vehicle control (VC) or ranolazine (Ran) in the presence or absence of insulin (n= 4-5). (**B**) PDH phosphorylation and PDH from C2C12 treated with VC or Ran (10 μM) (n=6). Values represent mean ± SEM.

Supplemental Figure 4



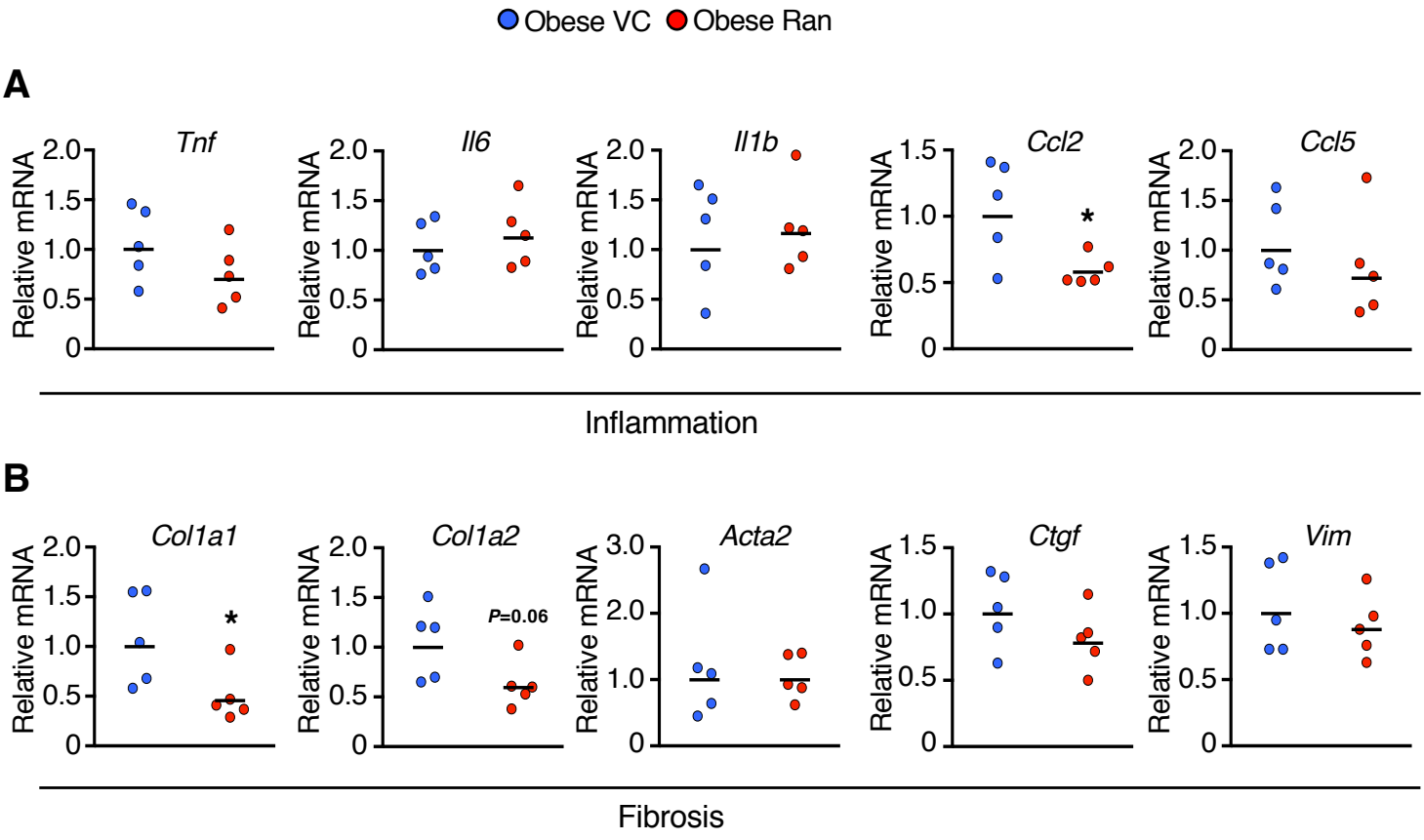
Supplemental Figure 4. Ranolazine treatment decreases PPARα target gene mRNA expression in obese mice. Lean and obese mice treated with either vehicle control (VC) or ranolazine (Ran) for 30-days, (**A**) *Slc27a1* (**B**) *Slc27a6* (**C**) *Acox1* (**D**) *Cd36* and (**E**) *Acadm* (n = 4-5). Values represent means ± SEM. Differences were determined using a two-way ANOVA, followed by a Bonferroni post-hoc analysis. **P* < 0.05, Significantly different from VC counterpart.

Supplemental Figure 5



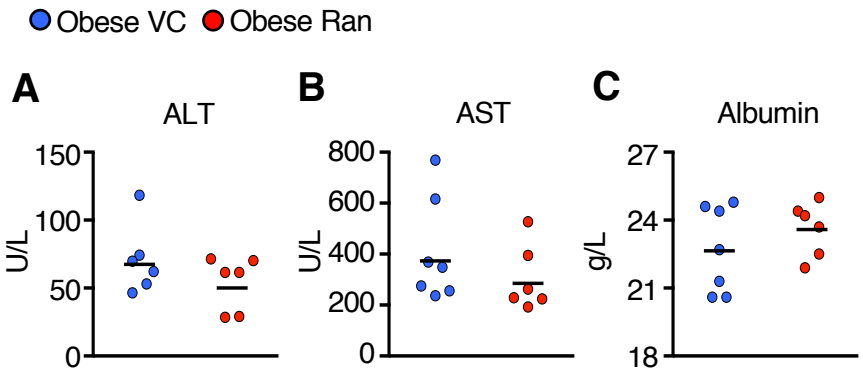
Supplemental Figure 5. Plasma glucagon levels in obese mice.
Obese mice treated with vehicle control (VC) or ranolazine (Ran) were fasted overnight and circulating glucagon levels were measured in plasma collected from tail whole-blood prior to a pyruvate tolerance test (n = 4-5). Values represent means ± SEM.

Supplemental Figure 6



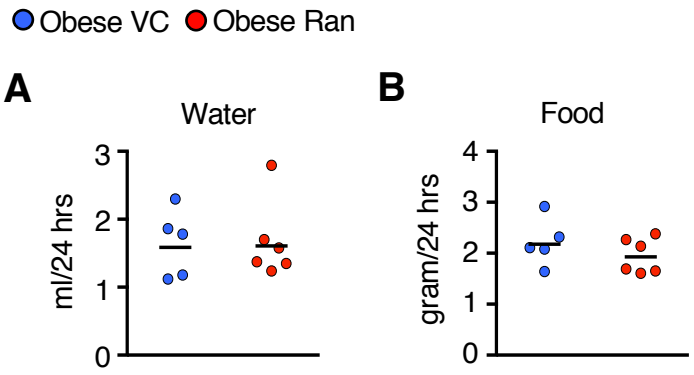
Supplemental Figure 6. Proinflammatory and profibrotic target gene mRNA expression in obese mice livers. (**A**) Markers of inflammation in livers from obese mice treated with vehicle control (VC) or ranolazine (Ran) for 30-days. (**B**) Markers of fibrosis in livers from obese mice treated with VC or Ran for 30-days. (n = 5). Values represent means ± SEM. Differences were determined using an unpaired two-tailed Student's t-test. **P* < 0.05, Significantly different from VC counterpart.

Supplemental Figure 7



Supplemental Figure 7. Plasma markers in obese mice.
(**A**) ALT (**B**) AST and (**C**) Albumin plasma levels in obese mice treated with vehicle control (VC) or ranolazine (Ran) for 30-days (n = 6-7). Values represent means ± SEM. ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Supplemental Figure 8



Supplemental Figure 8. Water and food intake in obese mice. (**A**) Water and (**B**) food intake in obese mice treated with vehicle control (VC) or ranolazine (Ran) for 30-days (n = 5-6). Values represent means ± SEM.

Supplemental Table 1. Gene expression qPCR primers

Mouse gene primers

Gene Name	*Assay ID*
Acadm	Mm01323360_g1
Acox1	Mm01246834_m1
Slc27a1	Mm00449511_m1
Slc27a6	Mm01258609_m1
Cd36	Mm00432403_m1
Pdk1	Mm00554300_m1
Pdk2	Mm00446681_m1
Pdk4	Mm01166879_m1
Ppia	Mm02342430_g1

Gene Name	*Forward*	*Reverse*
Tnf	CATCTTCTCAAAATTCGAGTGACAA	TGGGAGTAGACAAGGTACAACCC
Il6	AGTTGCCTTCTTGGGACTGA	TCCACGATTTCCCAGAGAAC
Il1b	CCGTGGACCTTCCAGGATGA	GGGAACGTCACACACCAGCA
Ccl2	TACAAGAGGATCACCAGCAGC	ACCTTAGGGCAGATGCAGTT
Ccl5	TGCTGCTTTGCCTACCTCTC	TCTTCTCTGGGTTGGCACAC
Col1a1	TGCTAACGTGGTTCGTGACCGT	ACATCTTGAGGTCGCGGCATGT
Col1a2	TTGCTGAGGGCAACAGCAGGTT	AATGTCAAGGAACGGCAGGCGA
Acta2	CCCAGACATCAGGGAGTAATGG	TCTATCGGATACTTCAGCGTCA
Ctgf	TGACCCCTGCGACCCACA	TACACCGACCCACCGAAGACACAG
Vim	AGCAGTATGAAAGCGTGGCT	AAGGGCATCCACTTCACAGG
Actb	GTGACGTTGACATCCGTAAAGA	GCCGGACTCATCGTACTCC

Human gene primers

Gene Name	*Forward*	*Reverse*
PDK1	CTGTGATACGGATCAGAAACCG	TCCACCAAACAATAAAGAGTGCT
PDK2	ATGAAAGAGATCAACCTGCTTCC	GGCTCTGGACATACCAGCTC
PDK4	GGAGCATTTCTCGCGCTACA	ACAGGCAATTCTTGTCGCAAA
PPIA	CCCACCGTGTTCTTCGACATT	GGACCCGTATGCTTTAGGATGA