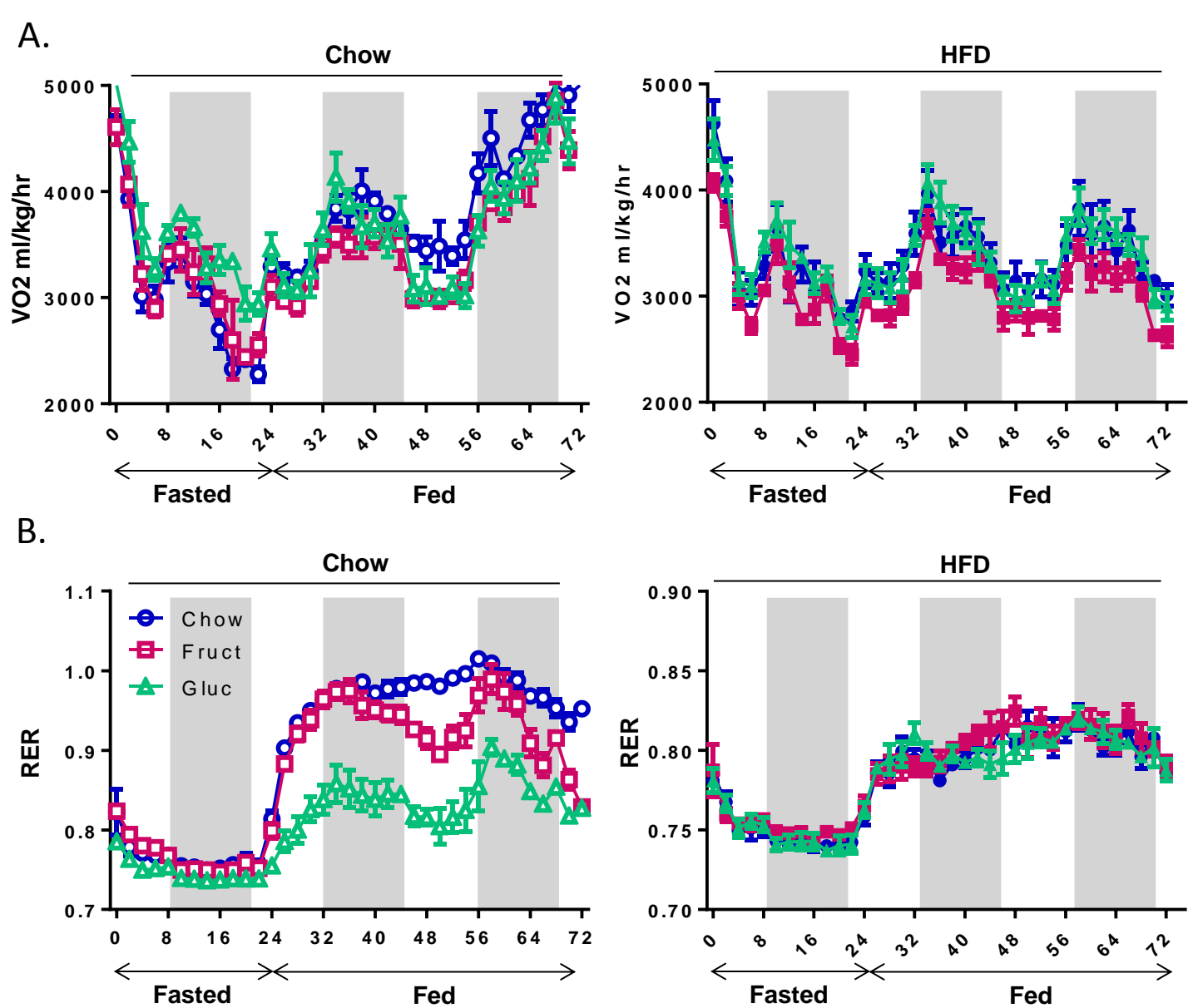


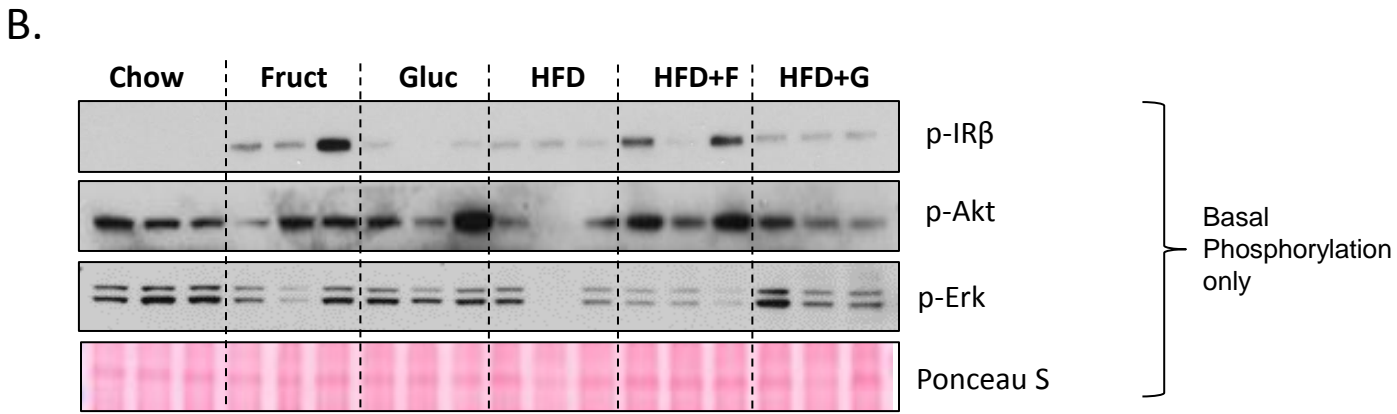
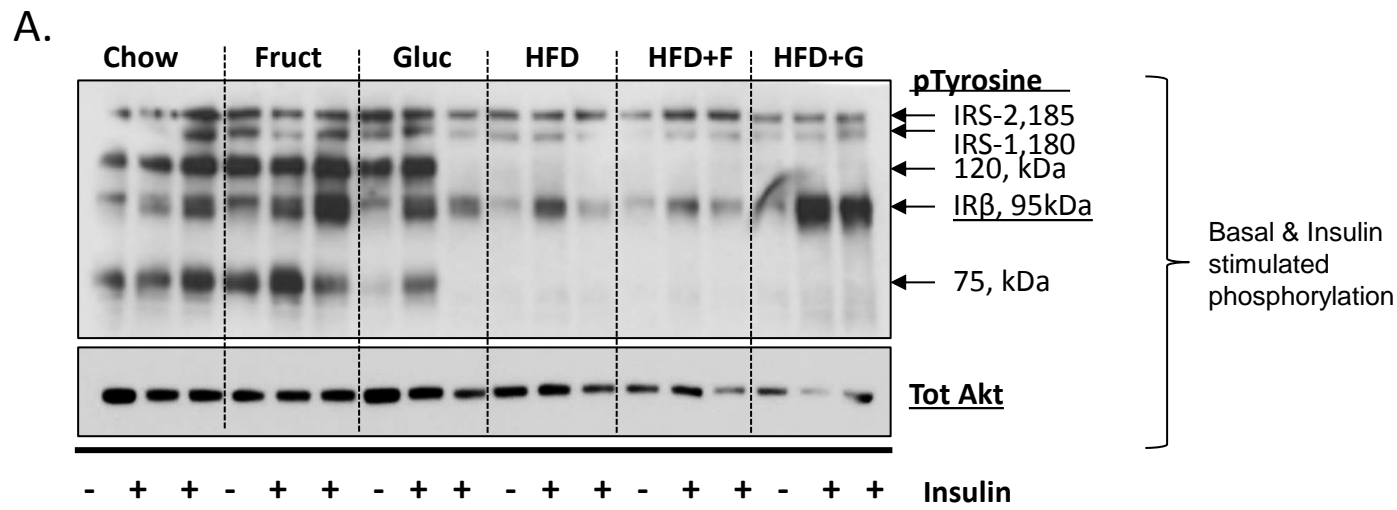
Sup. Fig. 1

A) Total caloric intake from both food (hashed bars) and water intake (black bars) was measured weekly and averaged over the 10 week study period. n=7-8 mice per group. B) Gross liver appearance of mice after 10 weeks on respective diets. Representative images are shown. n=7-8 mice per group. C) Percent subcutaneous fat and D) lean body mass was determined by dexa measurement of mice at 8 weeks on respective diets. E) Activity counts were measured in CLAMS cages during 24 hours of fasting, followed by 48 hours of refeeding. Statistical analysis was performed using two-way ANOVA with post hoc t-tests between the individual groups. # denotes significance as compared to Chow+H₂O group, * represents significance within chow or HFD groups.



Sup. Fig. 2

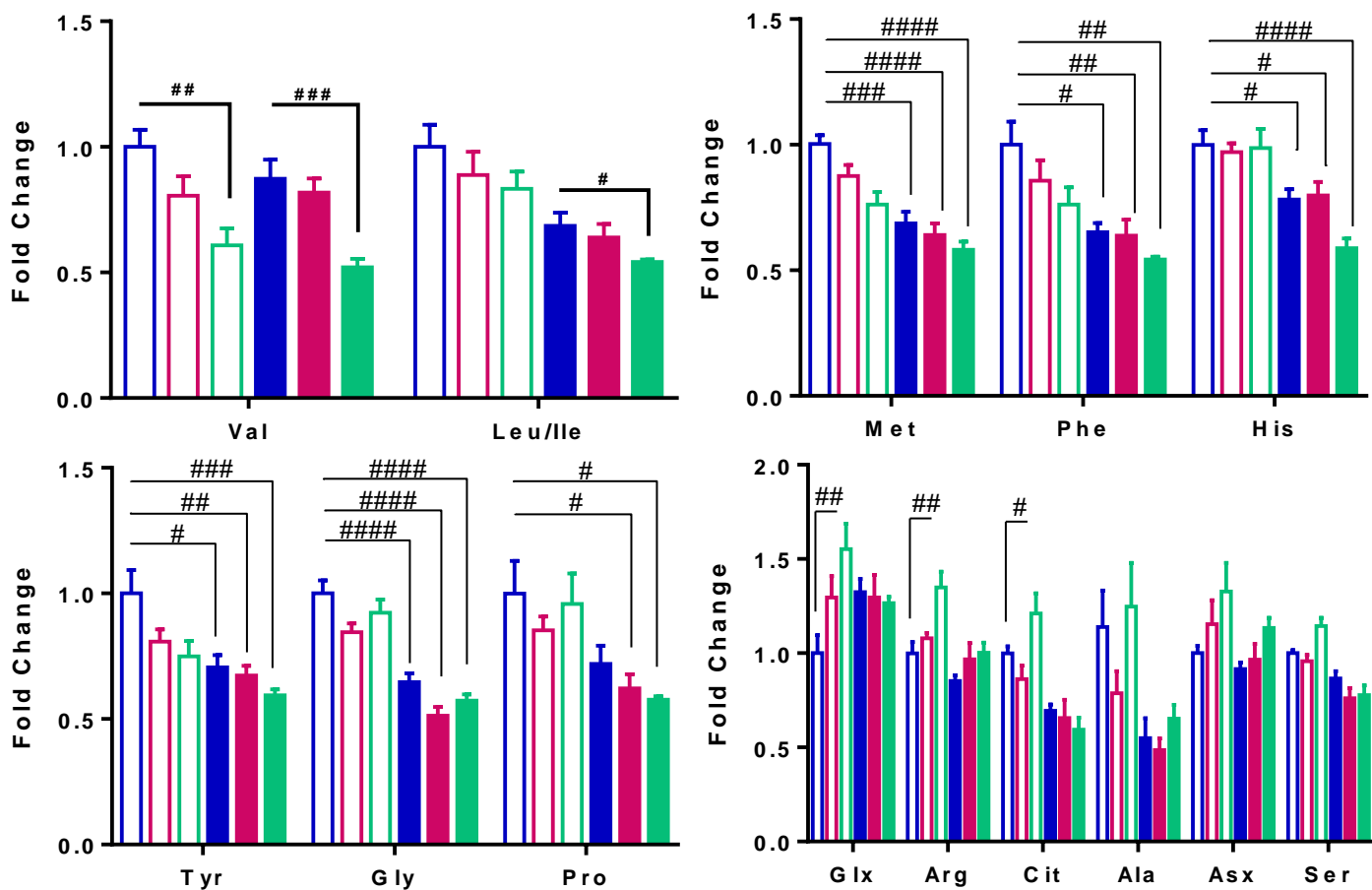
A) VO₂ and B) RER as assessed by comprehensive lab animal monitoring system (CLAMS) in mice after 8 weeks on diet, measured first during 24hours of fasting followed by 48 hours of refeeding. n=7-8 mice per group.



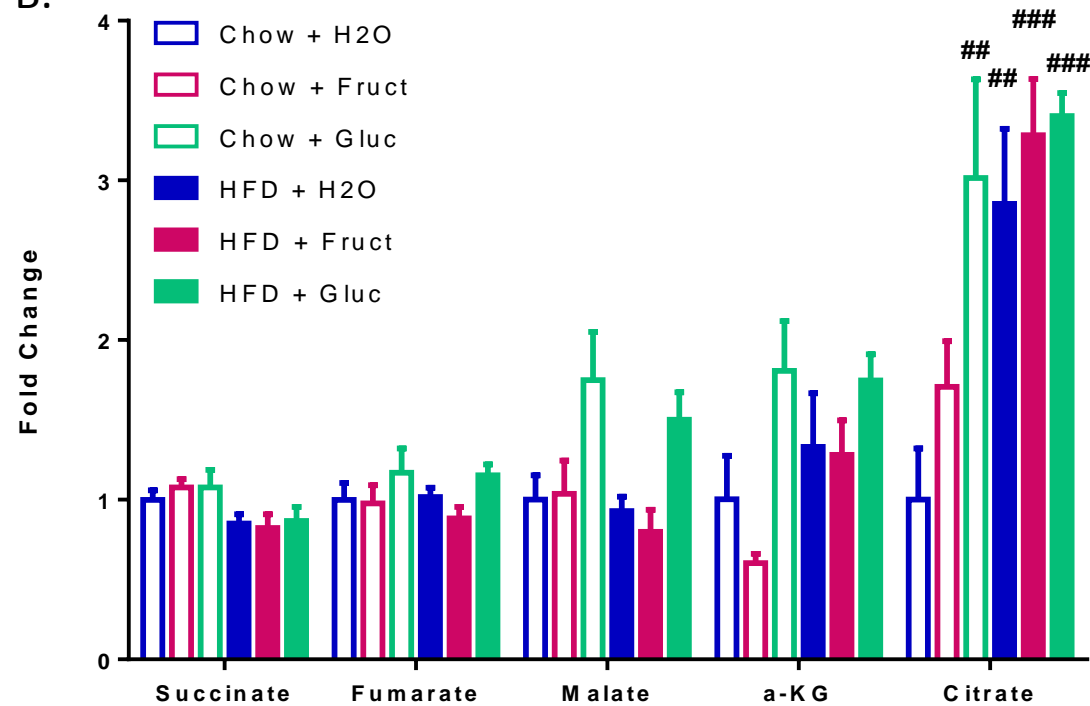
Sup. Fig. 3

After 10 weeks on diets, mice were anesthetized and one half of mice was injected with PBS and the other half with 0.5 U of insulin via the portal vein. Mice were sacrificed 10 minutes later and livers were snap frozen in liquid nitrogen for subsequent analysis. A) Tyrosine phosphorylation of insulin signaling molecules in livers of PBS and insulin injected mice. B) Basal phosphorylation levels of IR- β , Akt and Erk in mice injected with PBS only. n = 6 mice per group.

A.



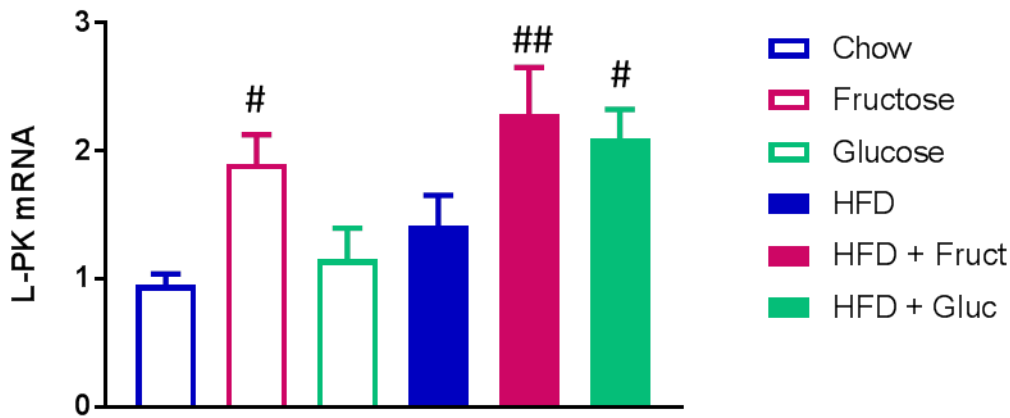
B.



Sup. Fig. 4

A) Amino acid levels measured from liver homogenates of mice after 10 weeks on diets. B) TCA cycle intermediates as measured from the same mice. n=6 mice per group. # denotes significance as compared to Chow+H₂O group.

A.



Sup. Fig. 5A

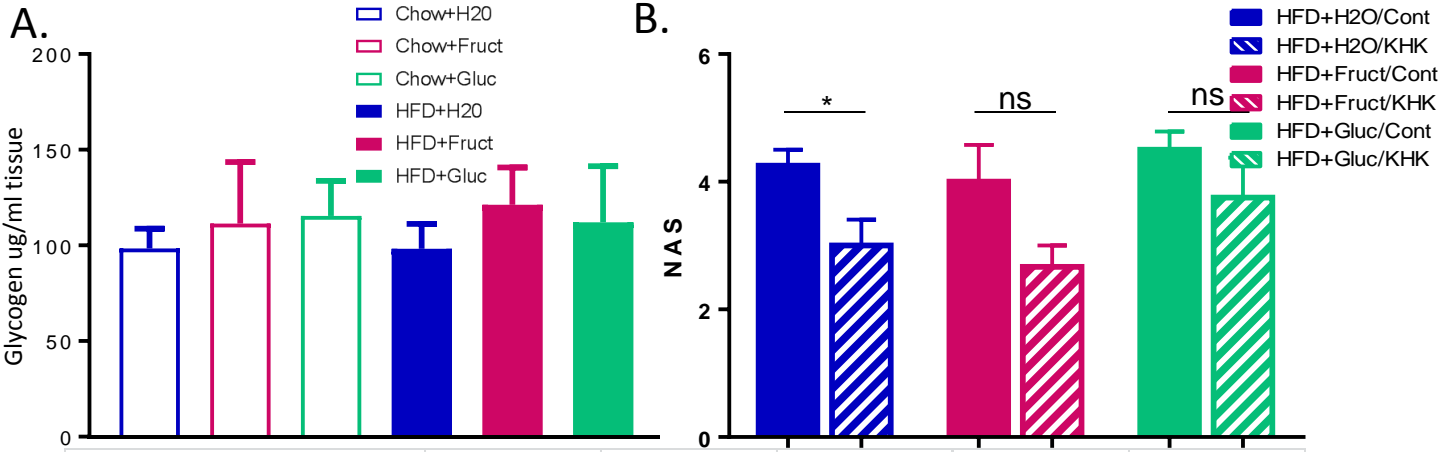
Hepatic mRNA expression of liver-pyruvate kinase in mice after 10 weeks on respective diets. n= 6 mice per group. # denotes significance as compared to Chow+H₂O group.

B.

Age	Weight Kg	BMI	NAS	Group
18.71	145.9	49.6	2	NoFL
18.29	137.4	40.0	0	
15.34	155.9	56.9	0	
19.07	177.5	61.5	0	
16.14	92.6	35.9	1	Steatosis
16.21	111.8	37.9	1	
18.84	121.1	45.9	2	
18.69	184.1	67.2	3	
18.78	136.3	43.0	6	NASH
17.01	151.0	47.2	5	
17.67	131.8	48.6	6	
19.29	225.8	70.1	4	

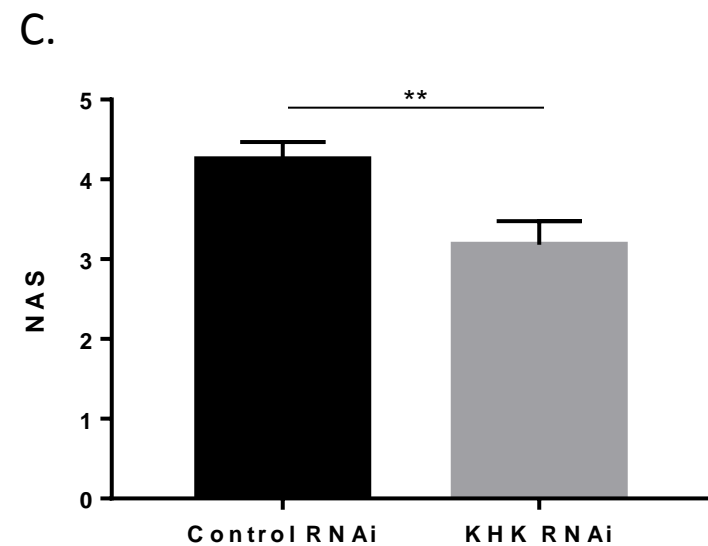
Sup. Fig. 5B

Clinical parameters and histologic assessment of liver biopsies from adolescent patients undergoing bariatric surgery. Samples were obtained from the Pediatric Obesity Tissue Repository in the Center for Bariatric Research and Innovation at Cincinnati Children's Hospital Medical Center. NAS and histological assessment was performed by pathologist at Cincinnati Children's Hospital Medical Center.



NAS SCORING

Diet	HFD	HFD+Fruct	HFD+Gluc	HFD	HFD+Fruct	HFD+Gluc
KHK Rnai	No	No	No	Yes	Yes	Yes
# examined	4	4	4	4	4	4
Steatosis						
1	0	0	0	0	1	0
2	0	2	1	3	2	1
3	4	2	3	1	1	3
Ballooning						
1	1	2	1	0	1	1
Inflammation						
1	4	4	2	3	3	3
2	0	0	2	0	1	0
Average NAS	4.3 ±0.3	4.0 ±0.6	4.5 ±0.3	3.0 ±0.4	2.7 ±0.3	3.8 ±0.6
Fibrosis	0.5	0.5	0.8	0.0	1.0	1.0

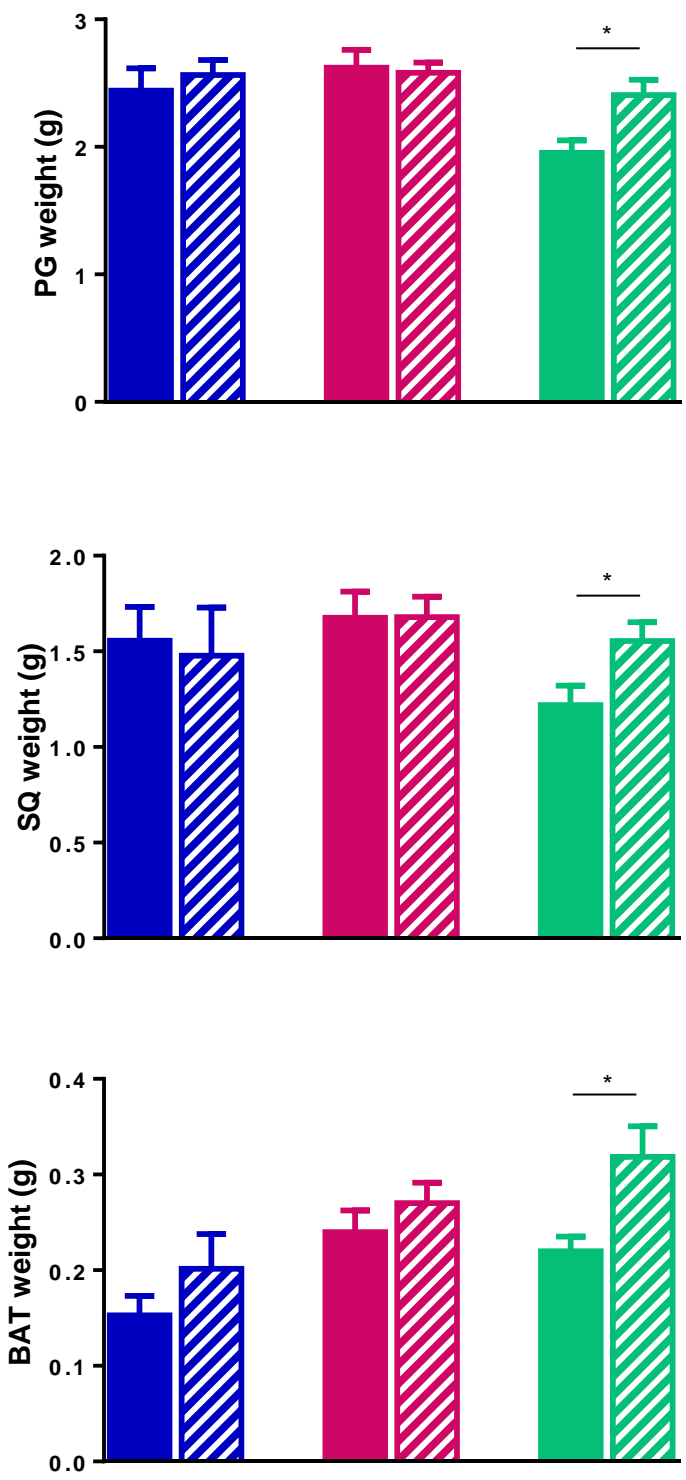


Group	Control	KHK
# examined	12	12
Steatosis		
1	0	1
2	4	6
3	8	5
Ballooning		
1	4	2
Inflammation		
1	10	9
2	2	1
Average NAS	4.3 ±0.2	3.2 ±0.3
Fibrosis	0.6	0.5

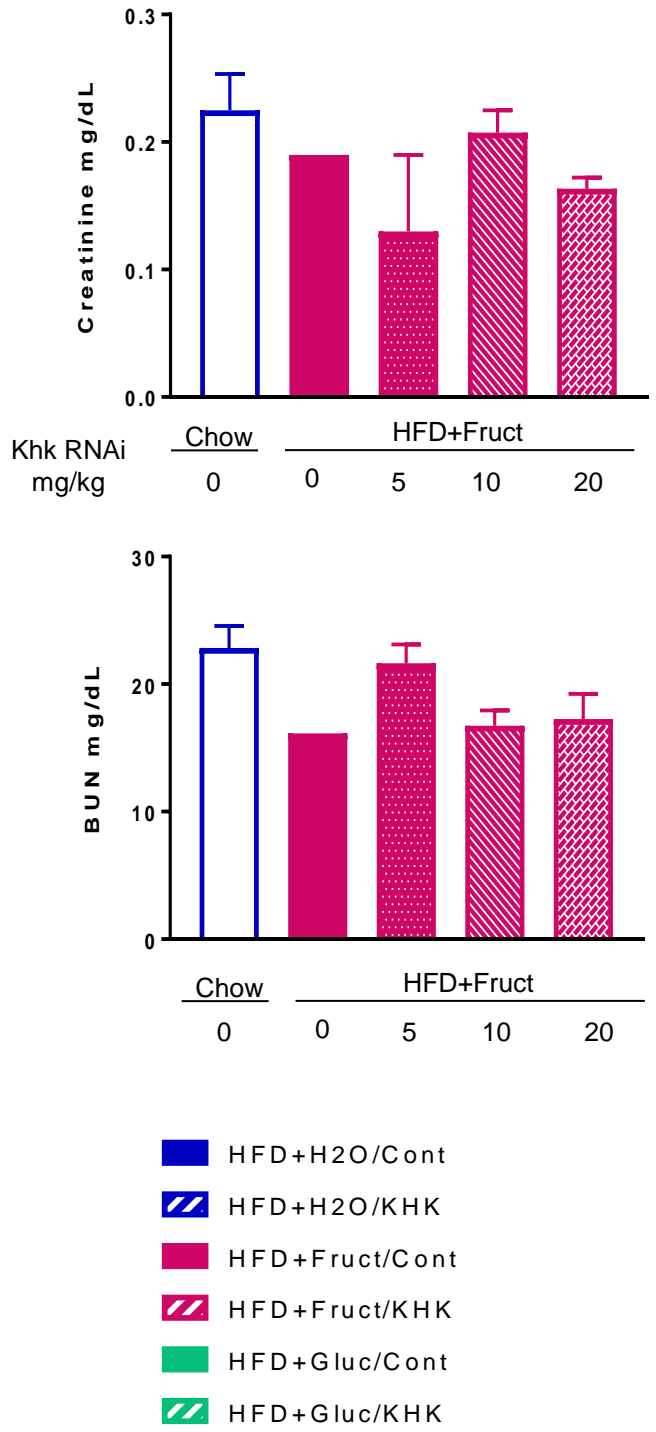
Sup. Fig. 6

A) Liver glycogen content from the mice after 10 weeks on the diet. Nonalcoholic fatty liver disease activity score (NAS) was assessed by certified veterinary pathologist at Alnylam Pharmaceuticals, blinded to the experimental conditions. B) NAS as calculated for each group and by C) combining all control and all Khk RNAi treated mice into two groups.

A.



B.



Sup. Fig. 7

A) Perigonadal (PG), subcutaneous (SQ) and brown adipose tissue (BAT) weights in mice treated with KHK or scramble RNAi for 4 weeks and being on respective diets for 10 weeks. n = 6 mice per group. B) Serum BUN and creatinine levels of chow and HFD+Fruct mice treated with either 0, 5, 10 or 20 mg/kg of Khk-C RNAi. # denotes significance as compared to Chow+H₂O group, * represents significance within chow or HFD groups.