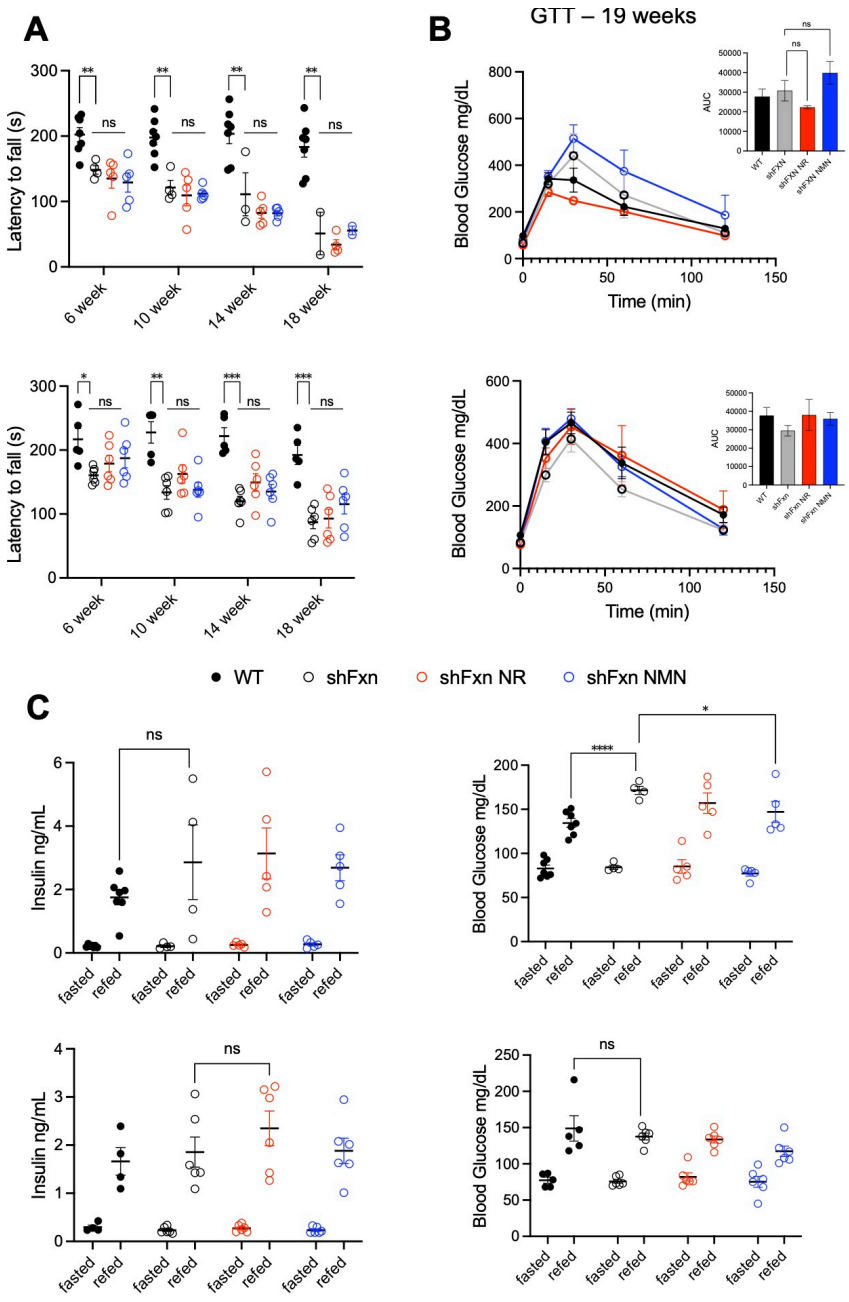
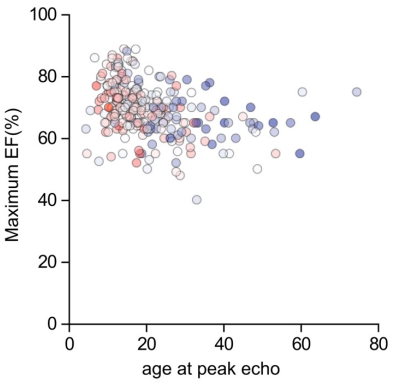
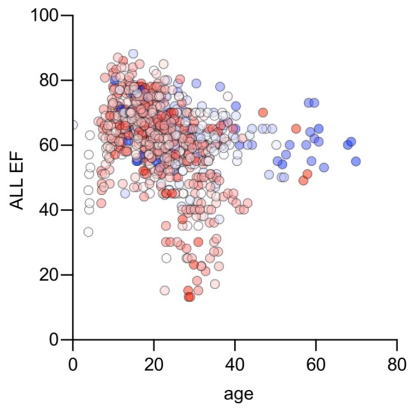


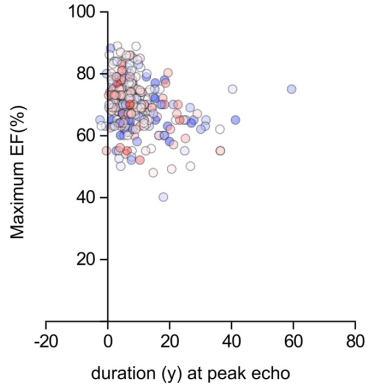
Figure S1. Treatment with NAD⁺ precursors does not consistently affect rotarod performance or glucose homeostasis in shFXN mice. (a) Latency to fall on rotarod in males (top) and females (bottom) (n=2-17) (b) Glucose tolerance test at 19 weeks post-doxycycline (n=3-7) (b, insets) Area under curve for respective GTT (c) Fasting and 4-hour refed insulin and blood glucose levels (n=4-7). (a, c: Two-Way ANOVA) (b): One-Way ANOVA) (*=p≤.05, **=p≤0.01, ***=p≤0.001, ****=p≤0.0001)

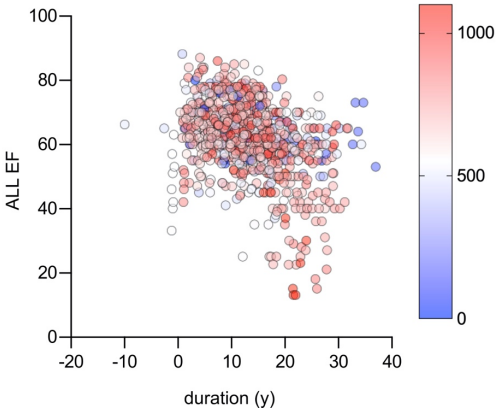
A





B





C

Characteristics	FRDA individuals with Maximal Echo record (N=323)
Age of onset	11.7±7.1
Male sex	157 (48.6)
GAA repeat length	674±217
Age at record	20.3±11.2

Heart Medication Usage	Individuals with FRDA (N=338)
ALL	127 (37.6)
ACE Inhibitors	54 (15.9)
Angiotensin II Inhibitors	4 (1.2)
Anticoagulants	36 (10.7)
Beta blockers	88 (26)
Ca^{2+}-channel blockers	14 (4.2)
Cholesterol-lowering medications	17 (5.0)
Diuretics	11 (3.3)
Other	15 (4.4)

Figure S2. High EFs are common in adolescents with FRDA while lower EFs are generally seen between 20 and 40 years of age. (a) Maximal EF (top) and all EFs recorded over 6+ years (bottom) according to age at echocardiogram (n=330 top, n=106 bottom) (b) Maximal EF (top) and all EFs recorded over 6+ years (bottom) according to disease duration (time since diagnosis) at echocardiogram (n=330 top, 106 bottom). (c) Clinical characteristics of FRDA dataset (top) and heart medication usage tabulation (bottom) in large cohort (n=338)

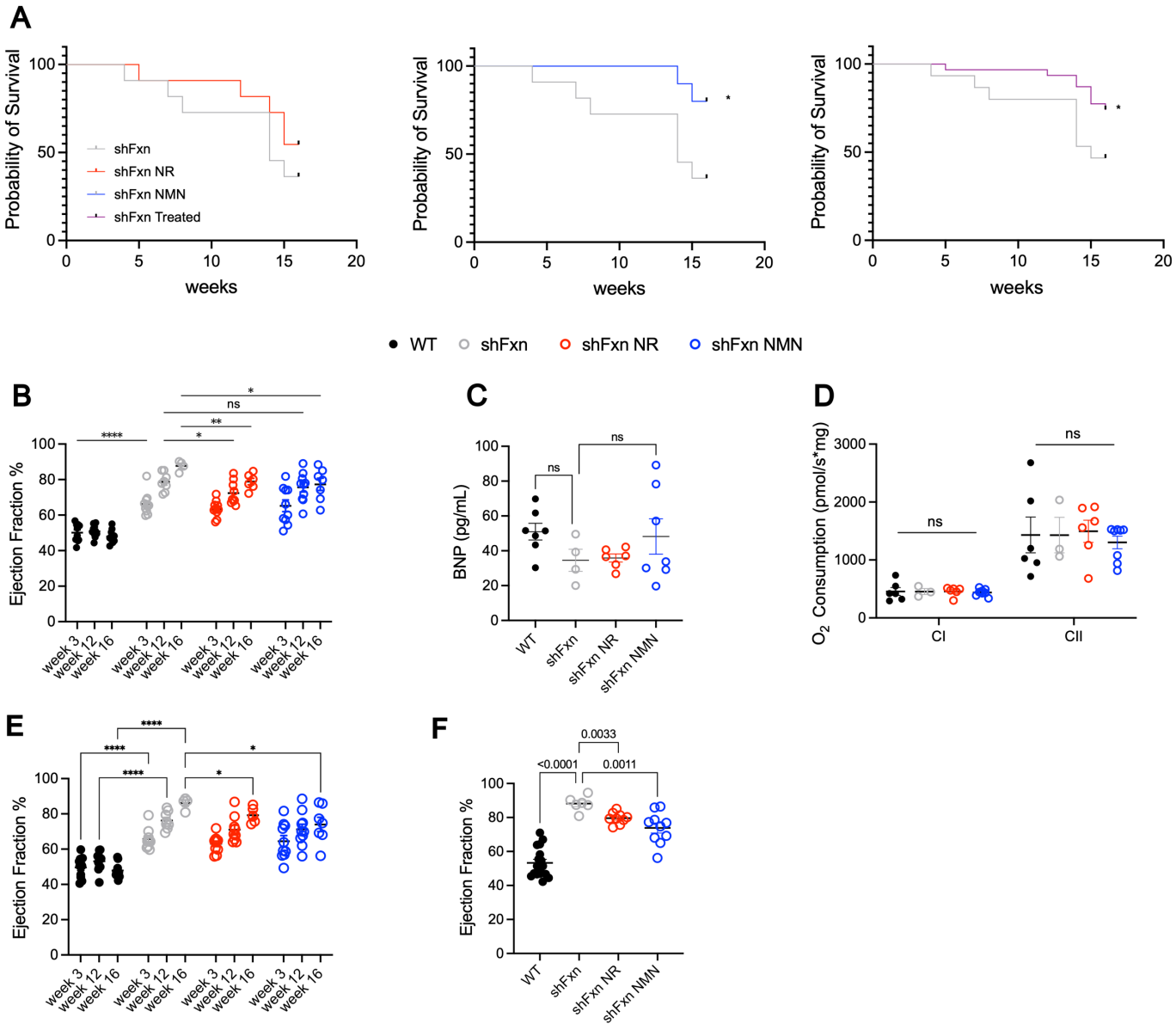


Figure S3. Analyses restricted to the 16-week cohort and short axis only measurements (a) Male shFxn survival curves with treatment (left, center: n=10-11, cohort 2 only, right: n=15-31 all treated) (b) Ejection fraction at 3, 12, and 16 weeks post-doxycycline (n=4-10) (c) BNP Levels in plasma at 16 weeks post-doxycycline (n=4-8) (d) Liver mitochondrial complex I and complex II respiration (n=3-8) (e) longitudinal measurement of ejection fraction calculated with short axis measurement only (f) Ejection fraction at 16-18 weeks calculated with short axis only. (a: Pairwise Mantel-Cox test for Survival) (b,d,e: Two-Way ANOVA) (c,f: One-Way ANOVA). (*=p≤.05, **=p≤0.01, ***=p≤0.001, ****=p≤0.0001)

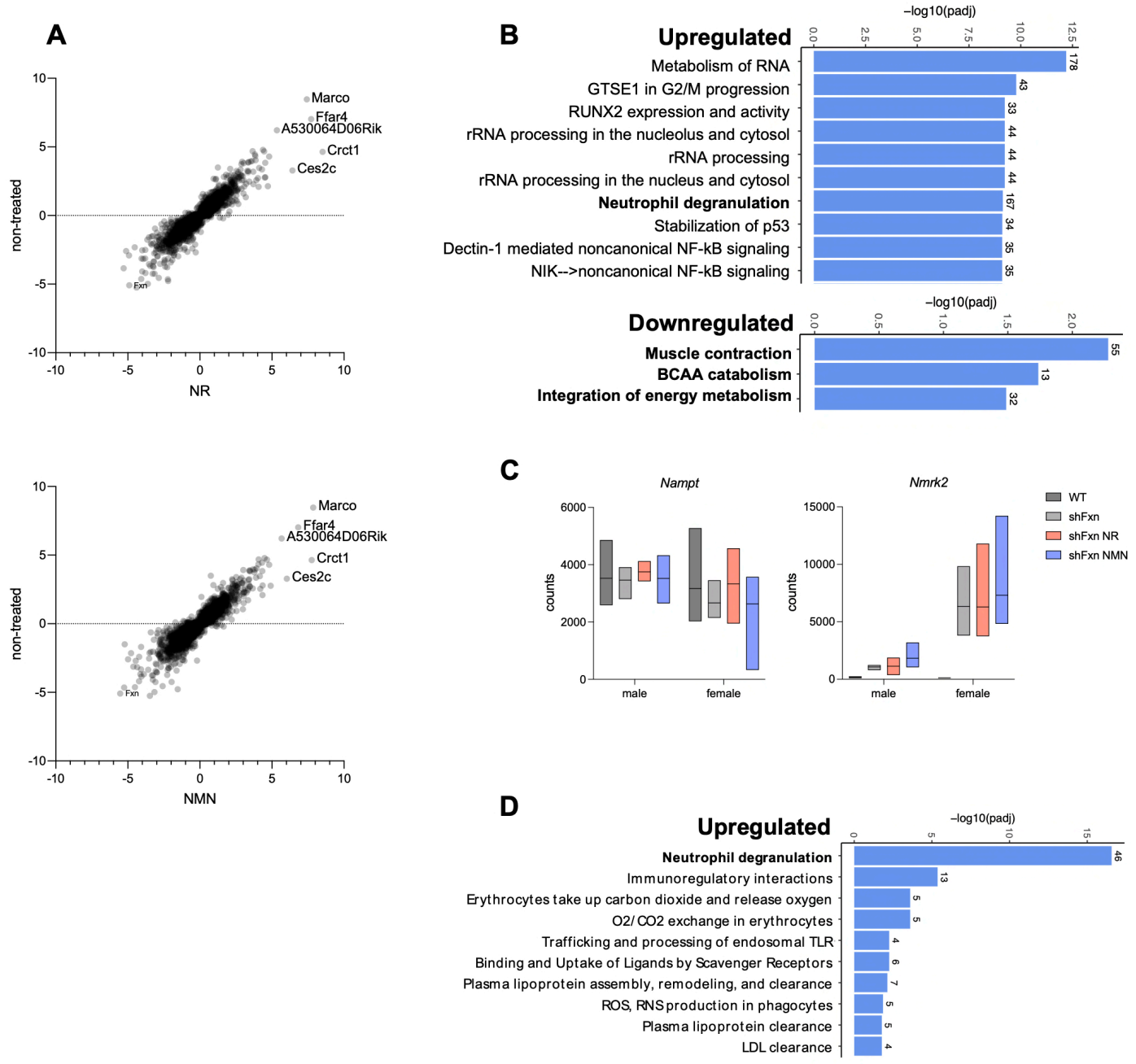
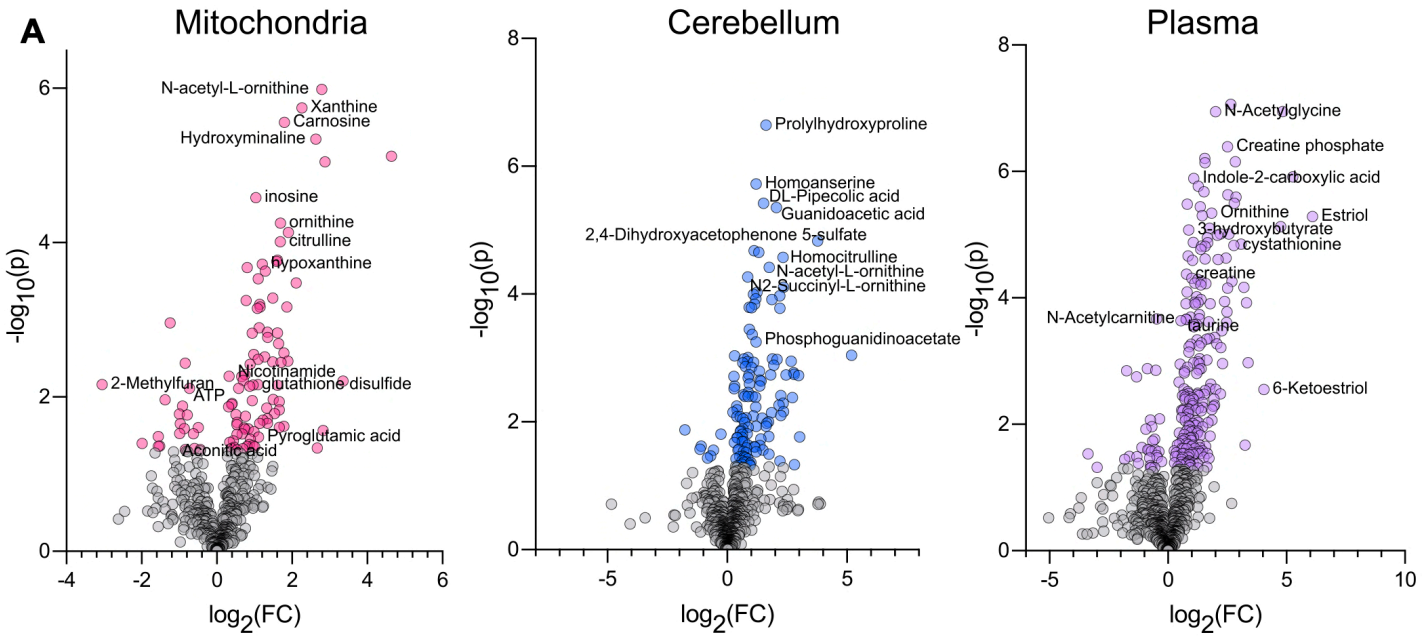


Figure S4. Transcriptomic signatures in shFxn mice. (a) Non-treated versus NR (top) and NMN (bottom) log_2(FC) relative to WT. (b) Upregulated and downregulated reactome terms in female shFxn mice (shFxn vs WT) (c) *Nmrk2* and *Nampt* levels in male and female mice (d) Upregulated terms in 20-week (experiment 1) versus 16-week (experiment 2) shFxn male mice.



B

	Metabolite	log_2(FC)	p
TCA	**pyruvate**	-0.20	ns
	citrate/isocitrate	0.10	ns
	alpha-ketoglutarate	-0.14	ns
	succinate	-0.57	2.0E-04
	fumarate	-0.67	9.2E-05
	malate	-0.67	5.4E-05
	aspartate	-0.64	ns
BCAA	**leucine/isoleucine**	-0.41	3.3E-02
	valine	-0.45	9.1E-03
	2 methyl 3 ketovaleric acid	-1.15	1.4E-02

Figure S5. Metabolomic profiles of heart mitochondria, cerebellum, and plasma (a) Volcano plot of mitochondria, cerebellum, and plasma (b) TCA and BCAA metabolites in heart tissue. (n=4-10, 2-tailed ttest, nominal p)

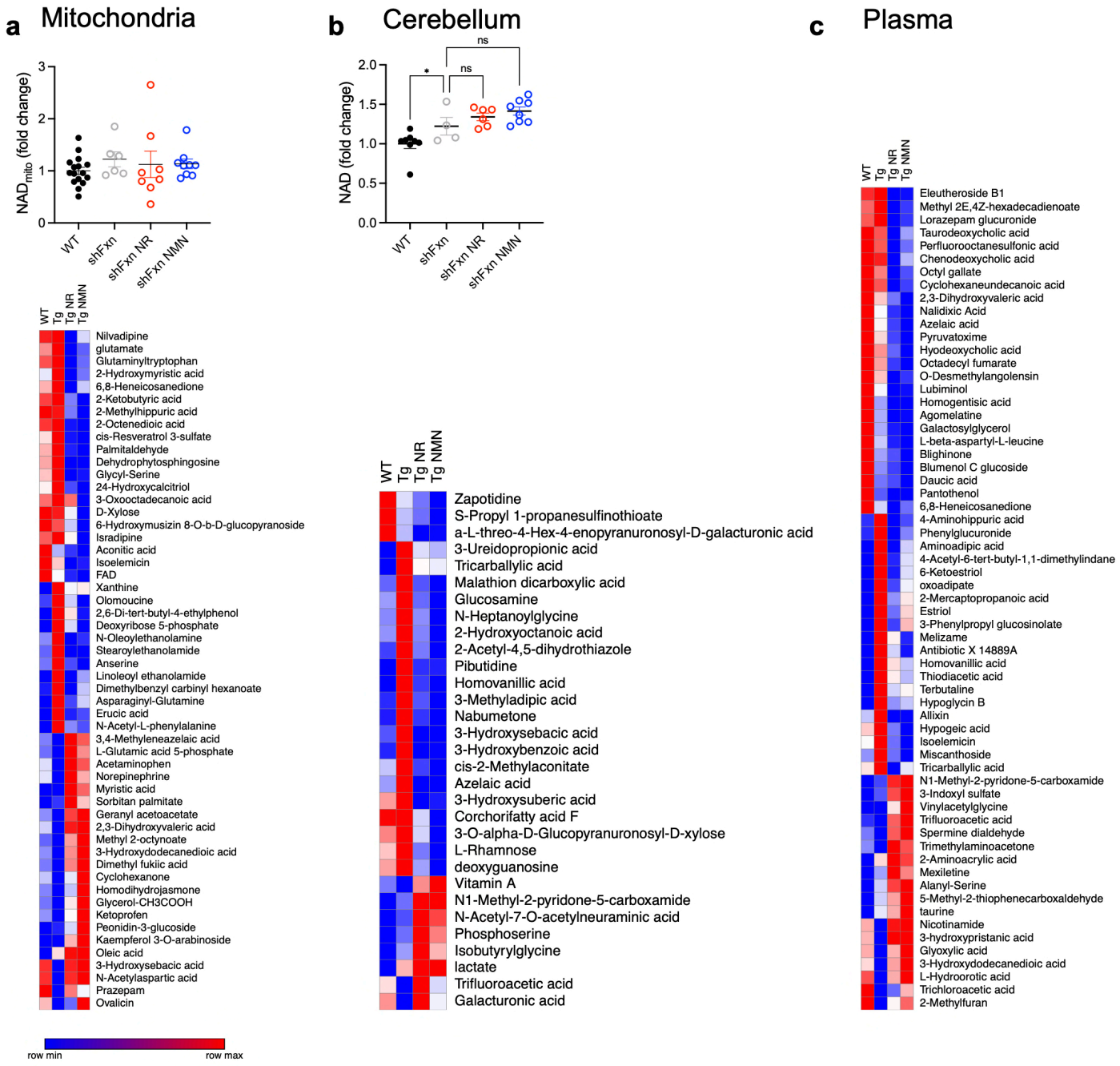
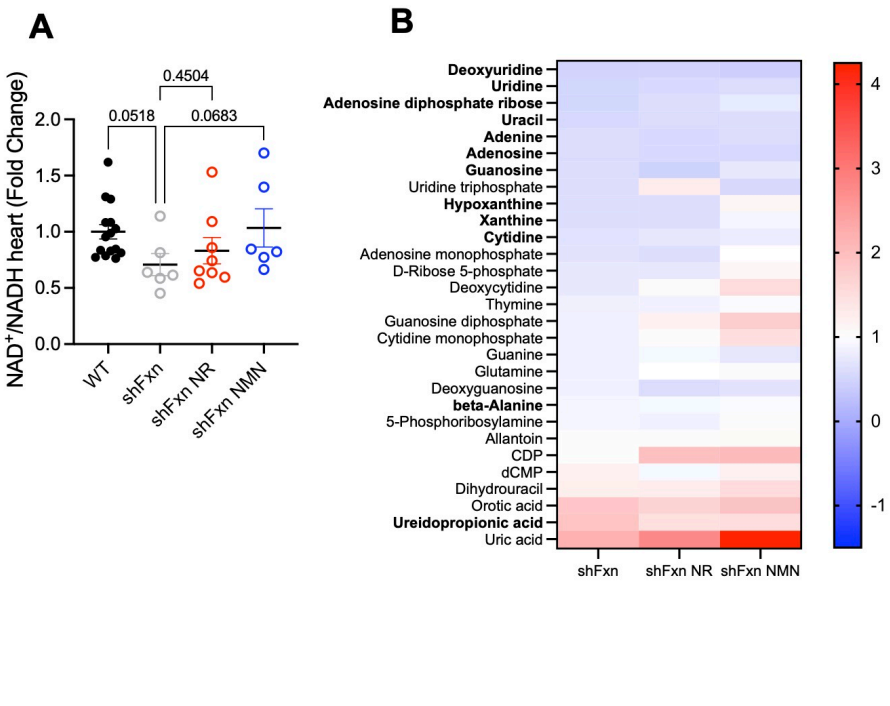


Figure S6. Metabolic effects of NAD precursor treatments in mitochondria, cerebellum, and plasma. (a) Mitochondrial NAD^+ 16-20 weeks post-doxycycline in males (b) Cerebellum NAD^+ 16 weeks post-doxycycline in males (c) NR and NMN changes in mitochondria, cerebellum, and plasma (n=4-10,normalized MS value, 2-tailed ttest nominal p) (*=p≤.05, **=p≤0.01, ***=p≤0.001, ****=p≤0.0001)



Nrf2 target	log_2(FC)	padj
Gclm	0.88	5.5E-08
Gclc	0.64	8.9E-10
Slc7a11	3.76	5.1E-05
Mthfd2	0.81	2.1E-02
Blvra	0.47	1.5E-03
Blvrb	0.92	2.7E-07
Hmox1	3.94	2.2E-109
Ftl1	1.33	1.0E-18
Gbe1	0.32	1.8E-02
Phgdh	0.86	3.8E-02
Hk3	2.04	1.0E-07
Srxn1	1.12	1.7E-11
Gsr	0.76	2.1E-08
Aldob	-1.04	1.9E-03
Pkm	-0.33	4.6E-04
Pfkl	-1.29	3.2E-47
Gpi1	-0.28	9.8E-03
Hk1	-0.34	2.0E-02
Hk2	-0.76	5.0E-09
Nqo1	-0.5	1.0E-03
Pgm5	-0.48	2.6E-03

Figure S7. Nrf2 targets are modified in shFxn mouse hearts. (a) NAD^+/NADH ratio in male shFxn hearts (n=6-15, One-Way ANOVA) (b) de novo nucleotide synthesis metabolites (bolded are significant in WT vs shFxn, n=4-8, Unpaired 2-tailed t-test) (c) Upregulated (red) and downregulated (blue) Nrf2 targets by counts (n=4-5, Wald Test)