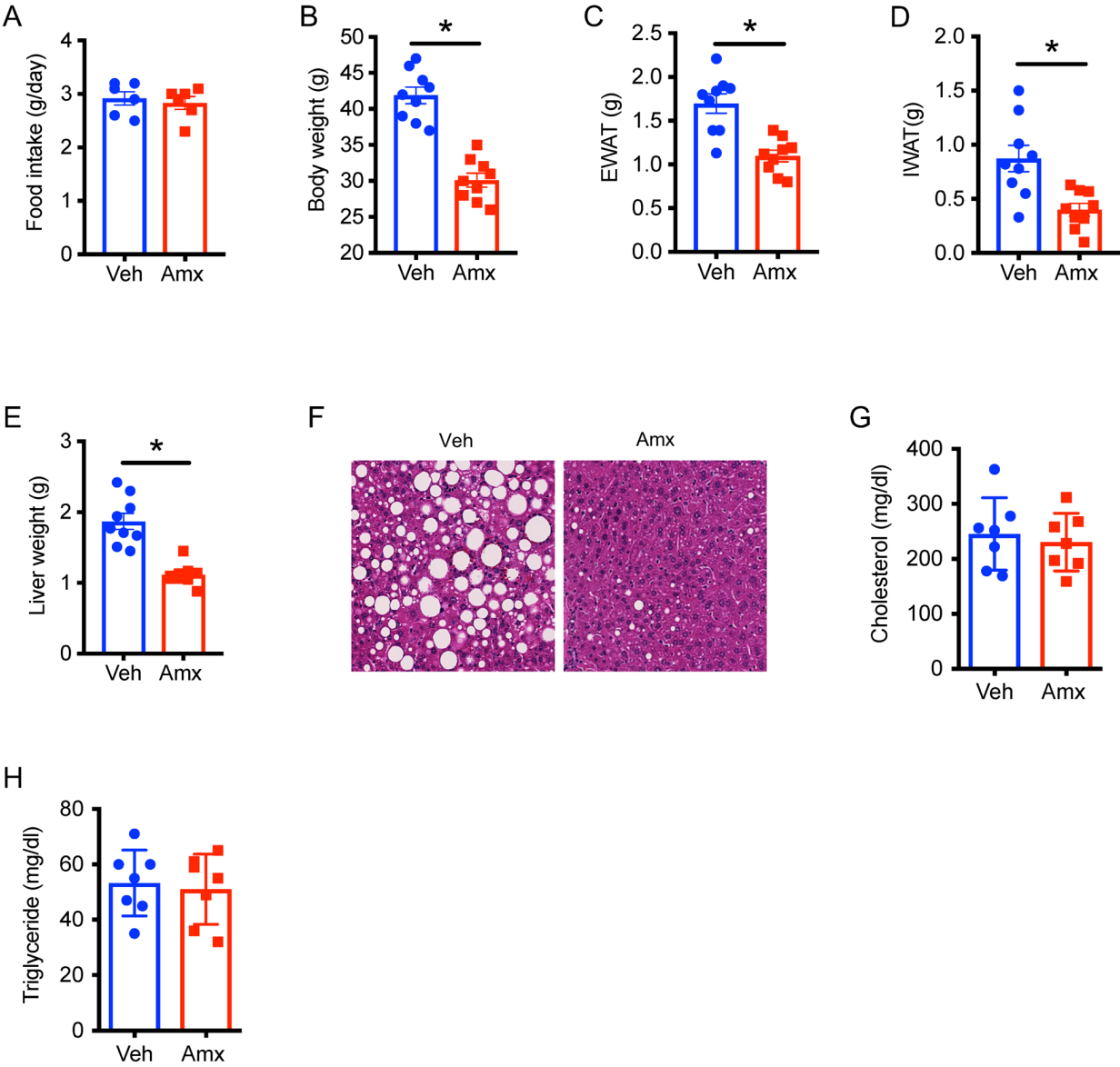
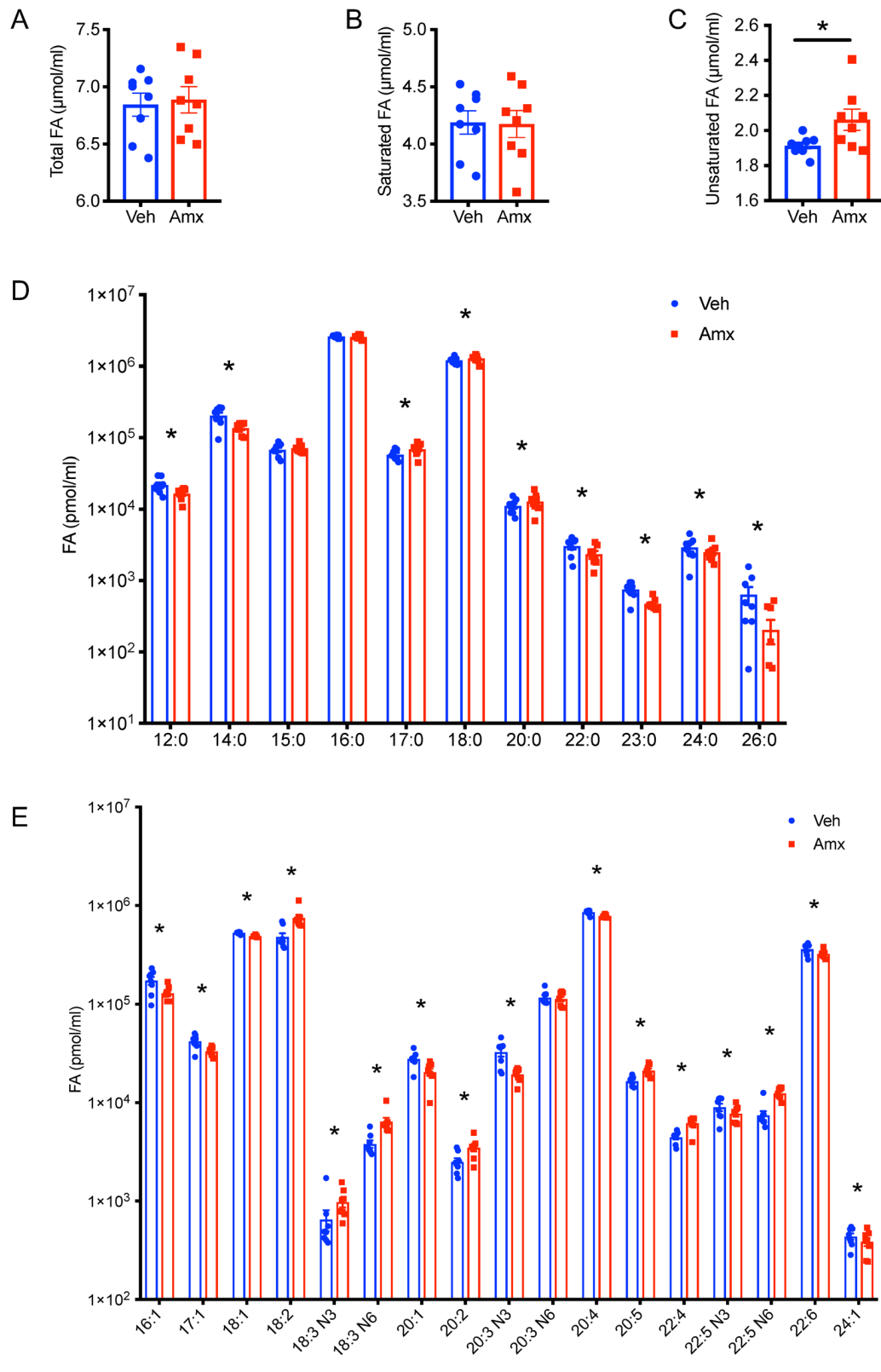


Supplementary Fig. 1



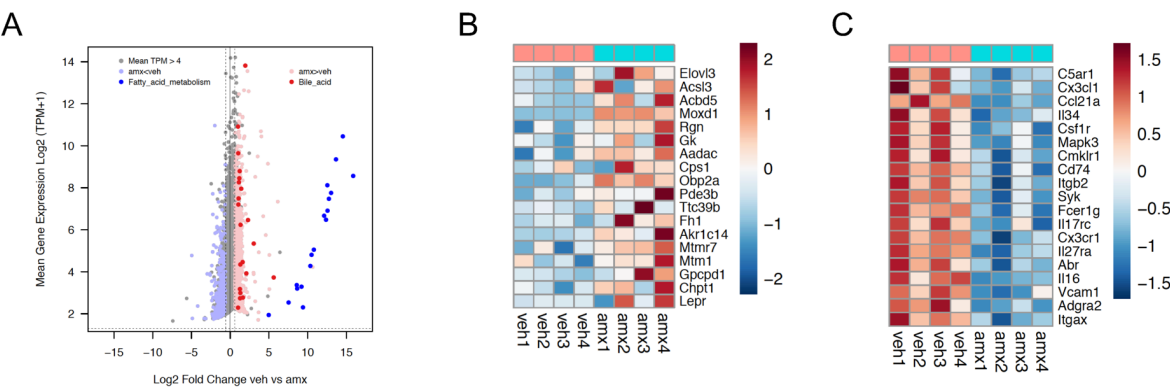
**Supplementary Figure 1. Amlexanox reduces body weight and fat mass in mice fed with Western diet. A-F.** *Ldlr*<sup>-/-</sup> mice were fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Food intake. **B.** Body weight. **C.** Weight of epididymal white adipose tissue. **D.** Weight of inguinal white adipose tissues. **E.** Liver weight. **F.** H&E staining of liver sections. **G-H.** *Ldlr*<sup>-/-</sup> mice were fed normal chow diet for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of chow diet feeding. **G.** Fasting serum cholesterol. **H.** Fasting serum triglyceride. Mean  $\pm$  SEM. \*,  $P < 0.05$ , Student's unpaired *t* test.

Supplementary Fig. 2



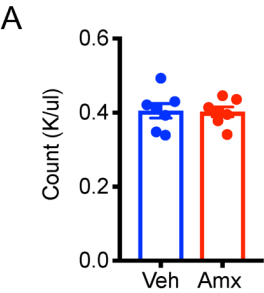
**Supplementary Figure 2. The effects of amlexanox on circulating levels of total fatty acids.** Lipidomic profiling of plasma from fasted *Ldlr*<sup>-/-</sup> mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Total fatty acids. **B.** Saturated fatty acids. **C.** Unsaturated fatty acids. **D.** Species of saturated fatty acids. **E.** Species of unsaturated fatty acids. Mean  $\pm$  SEM. \*,  $P < 0.05$ , Student's unpaired *t* test.

Supplementary Fig. 3



**Supplementary Figure 3. Amlexanox affects hepatic transcriptome.** Transcriptomic profiling of livers from *Ldlr*<sup>-/-</sup> mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** MA plot of RNA-seq data. **B, C.** Relative expression values (Z-scaled  $\log_2(\text{TPM}+1)$ ) for genes involved in fatty acid metabolism (B) or inflammation (C).

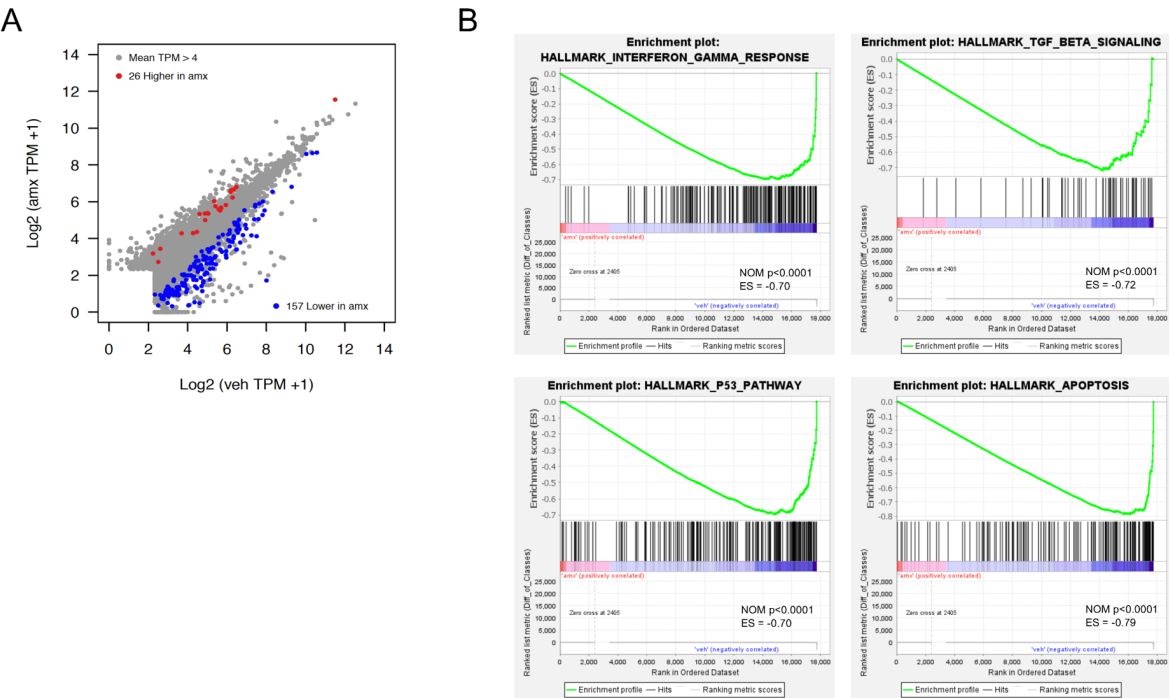
Supplementary Fig. 4



**Supplementary Figure 4. Amlexanox does not affect the number of circulating monocytes in mice fed chow diet.** Circulating monocytes in *Ldlr*<sup>-/-</sup> mice were fed normal chow diet for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of feeding.



Supplementary Fig. 5



**Supplementary Figure 5. Amlexanox affects transcriptome of aortic vessel.** Transcriptomic profiling of aorta from *Ldlr*<sup>-/-</sup> mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Scatterplot of RNA-seq data. **B.** Gene Set Enrichment Analysis of differentially expressed transcripts related to interferon gamma response, TGF $\beta$  signaling, P53 pathway and apoptosis in aorta of vehicle or amlexanox treated WD-fed *Ldlr*<sup>-/-</sup> mice.