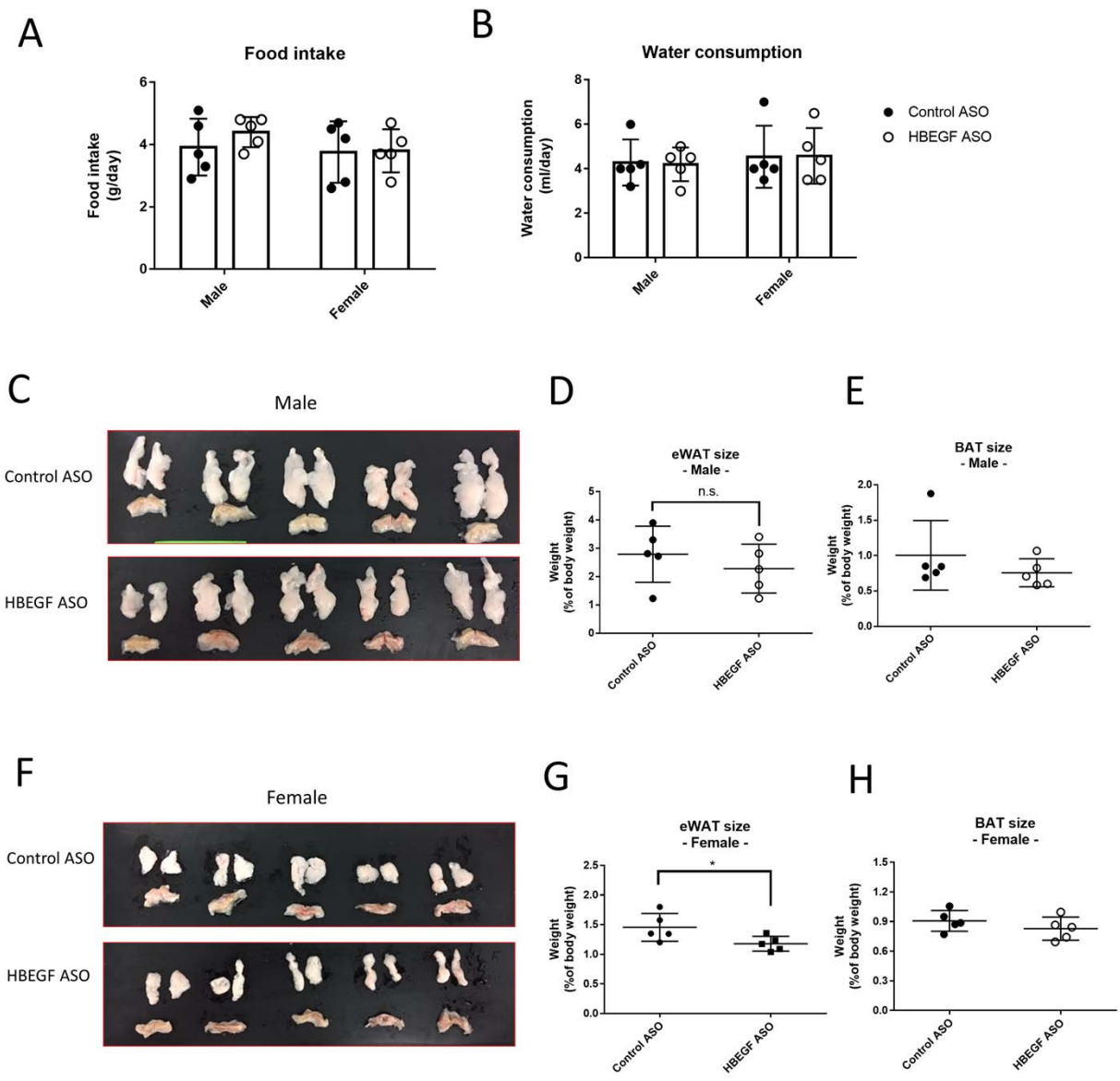
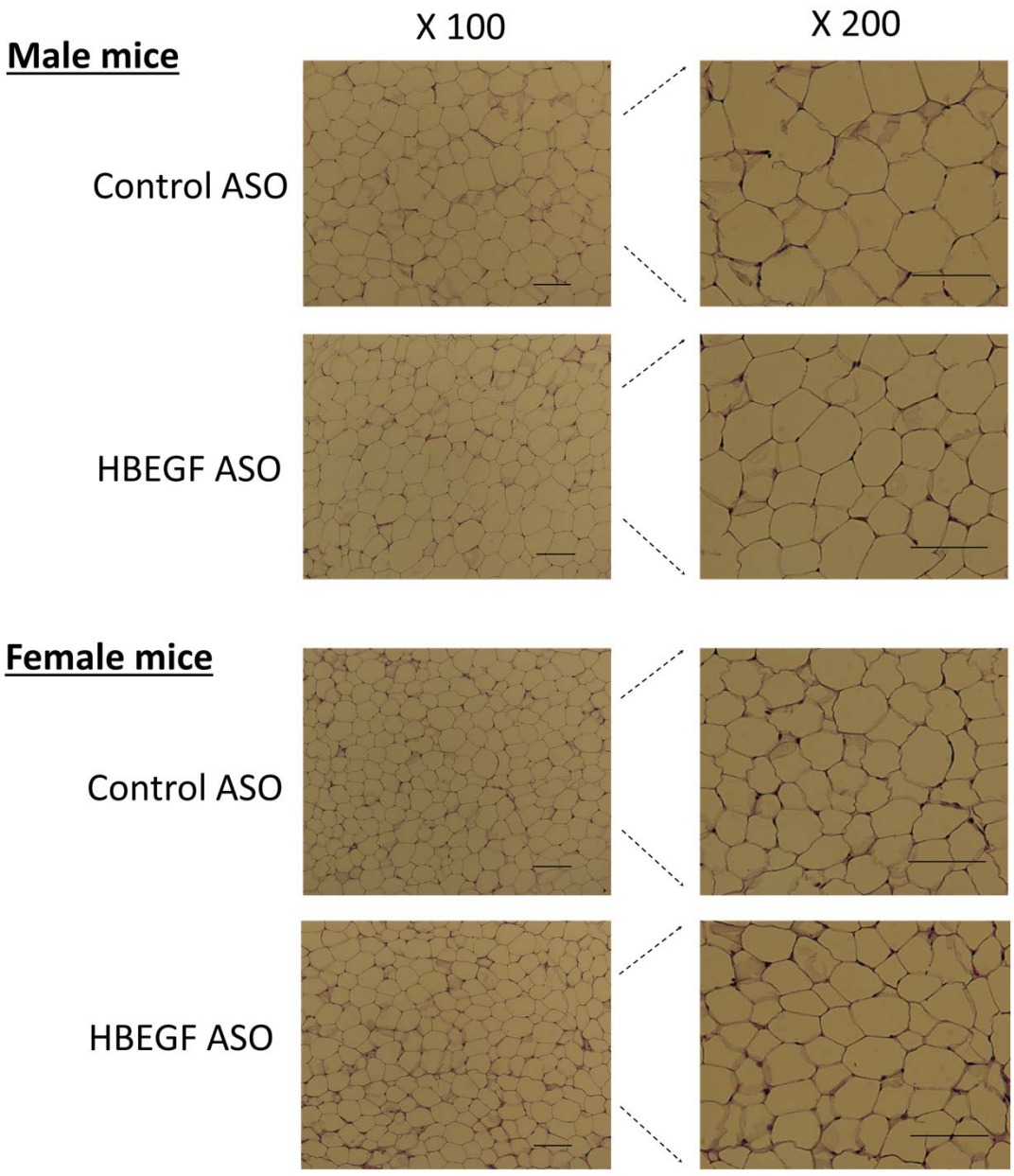
Supplemental Figure 1.



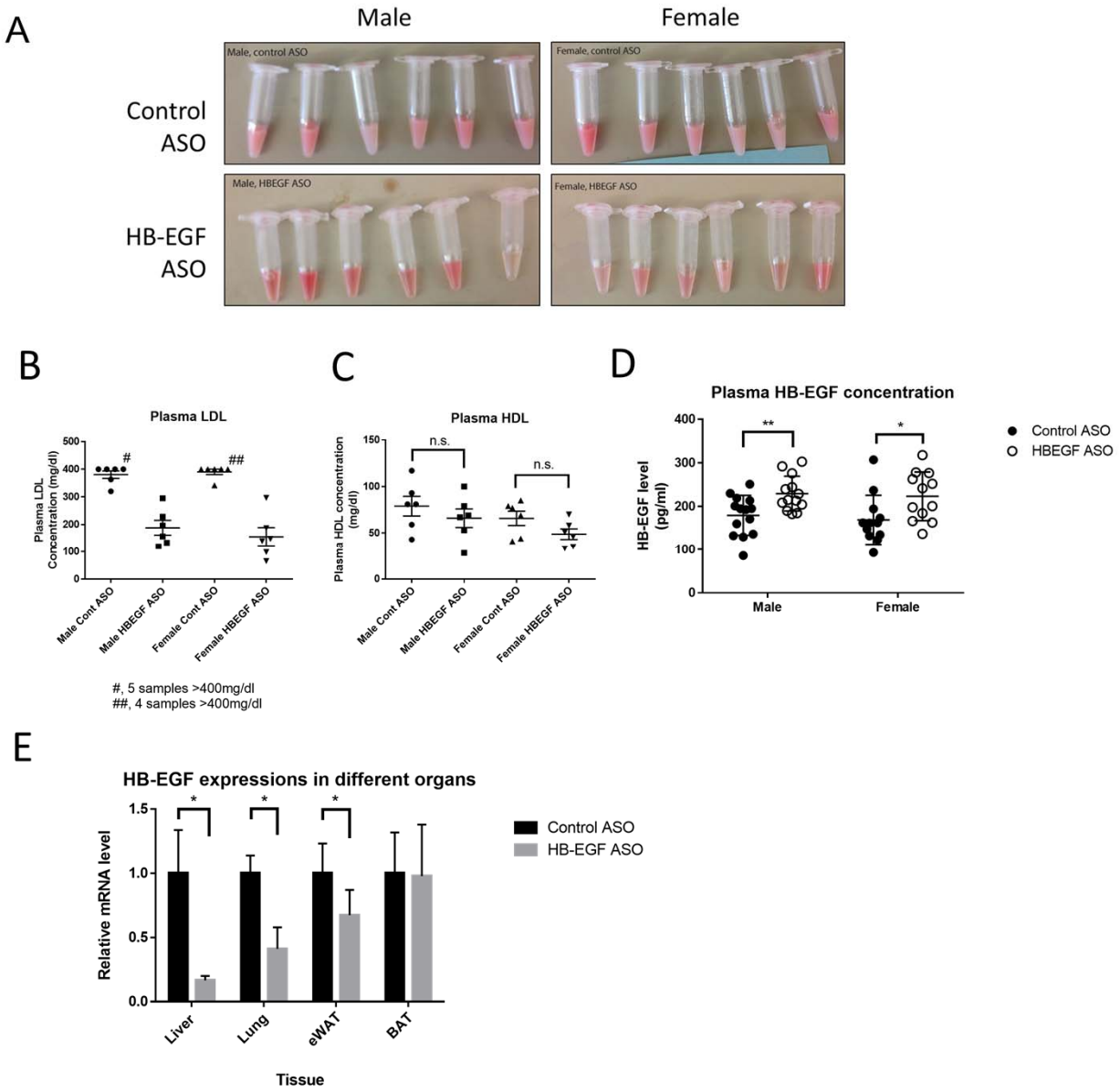
Supplementary Figure 1. The effects of the HB-EGF ASO administration on the food intakes and the size of the white and brown adipose tissues. (**A-B**) The male and female C57BL/6J mice at the age of 8 weeks were treated with the control and HB-EGF ASO administrations at the dose of 40 and 20mg/kg/week by the 2-week interval for total four weeks. The food and water intake were measured using metabolic cages. (**C-H**) The male and female C57BL/6J mice at the age of 8 weeks under the Western diet (21% fat, 0.2% cholesterol) were treated with the control and HB-EGF ASO administrations at the dose of 40 and 20mg/kg/week by the 2-week interval for total four weeks. At the termination step, the weight of the epididymal white adipose and interscapular brown adipose tissues in the male and female mice were measured. * < 0.05 and n.s. means no significance.

Supplemental Figure 2.



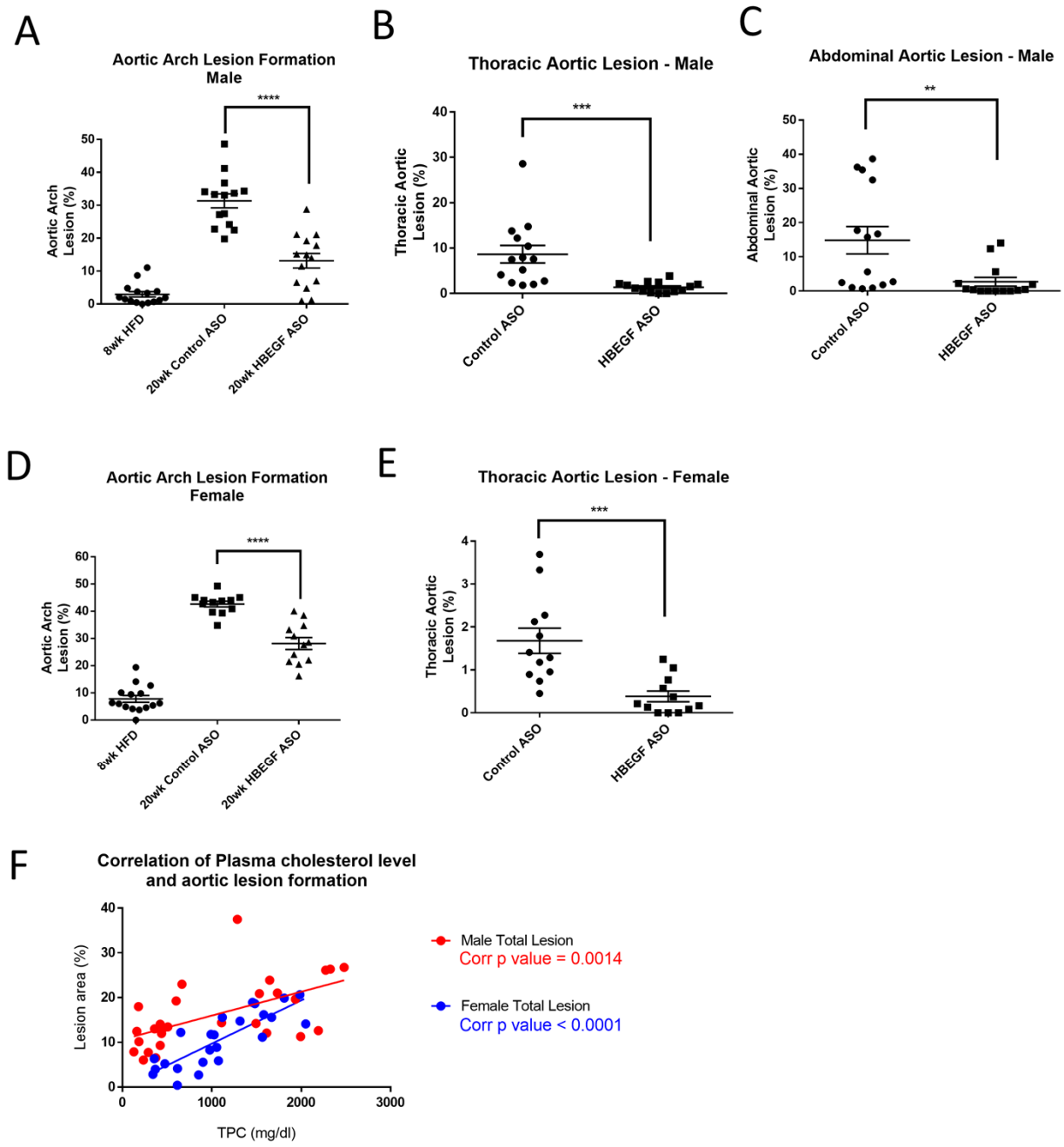
Supplementary Figure 2. HB-EGF ASO administration did not affect the size and morphology of the adipocytes in the epididymal white adipose tissue in male and female mice. The cell size and morphology of the eWAT tissues that are described in the Suppl. Figure 1 was examined using a standard procedure of the adipose tissue paraffin-embedded sectioning and Hematoxylin staining. The black bar inserted indicates the 100μm length.

Supplementary Figure 3



Supplemental Figure 3. HB-EGF ASO administration effectively downregulated circulatory lipid levels. Refer to **Figure 1A** for mouse treatment scheme. (**A**) Plasma samples were isolated at the termination step. The plasma samples from control ASO group were apparently opaque, while the plasma samples from the HB-EGF ASO group were translucent. (**B-C**) The concentration of low-density lipoprotein (LDL) (**B**) and high-density lipoprotein (HDL) (**C**) in plasma samples that are selected nearest the median range of cholesterol levels were quantified using commercial service (CPATH pathology core facility at the University of Missouri, Columbia). (**D**) The circulatory HB-EGF levels were measured in the plasma samples collected from the male and female LDLR deficient mice under Western diet and ASO treatment using a commercially available mouse HB-EGF ELISA kit. (**E**) The HB-EGF expression levels were compared in the liver, lung, white and brown adipose tissues in a control experiment. The hyperlipidemic mouse models were treated with control and HB-EGF ASO for six weeks, and the relative expression levels of the HB-EGF in the organs were compared. * $p<0.05$ and ** $p<0.01$, and n.s. means not significant.

Supplementary Figure 4.



Supplemental Figure 4. HB-EGF ASO administration effectively suppressed atherosclerotic lesion development in the aorta. Male and female LDLR deficient mice were fed high-fat diet (HFD) diet and injected with ASOs as described in Figure 1A scheme. (**A, D**) En face measurement of intimal lesion size in the aortic arch as a percent of the total aortic area for male and female. (**B, E**) Atherosclerotic lesion developments in the thoracic aortic area for male and female. (**E**) Abdominal aortic area lesion formation for male mice. Thoracic and abdominal aortic lesion area for the 8-week HFD pretreatment groups were negligible, thus, not quantified. The abdominal aortic lesion formation in the female mice was negligible as well, thus, not quantified. (**F**) Correlation plotting or each individual's total plasma cholesterol concentration and aortic arch lesion size in the aorta. The plot includes both control and HB-EGF ASO treatment groups for male and female mice. Male and female plasma samples were designated with different colors ** $p<0.01$, *** $p<0.001$, and **** $p<0.0001$.

Supplementary Figure 5

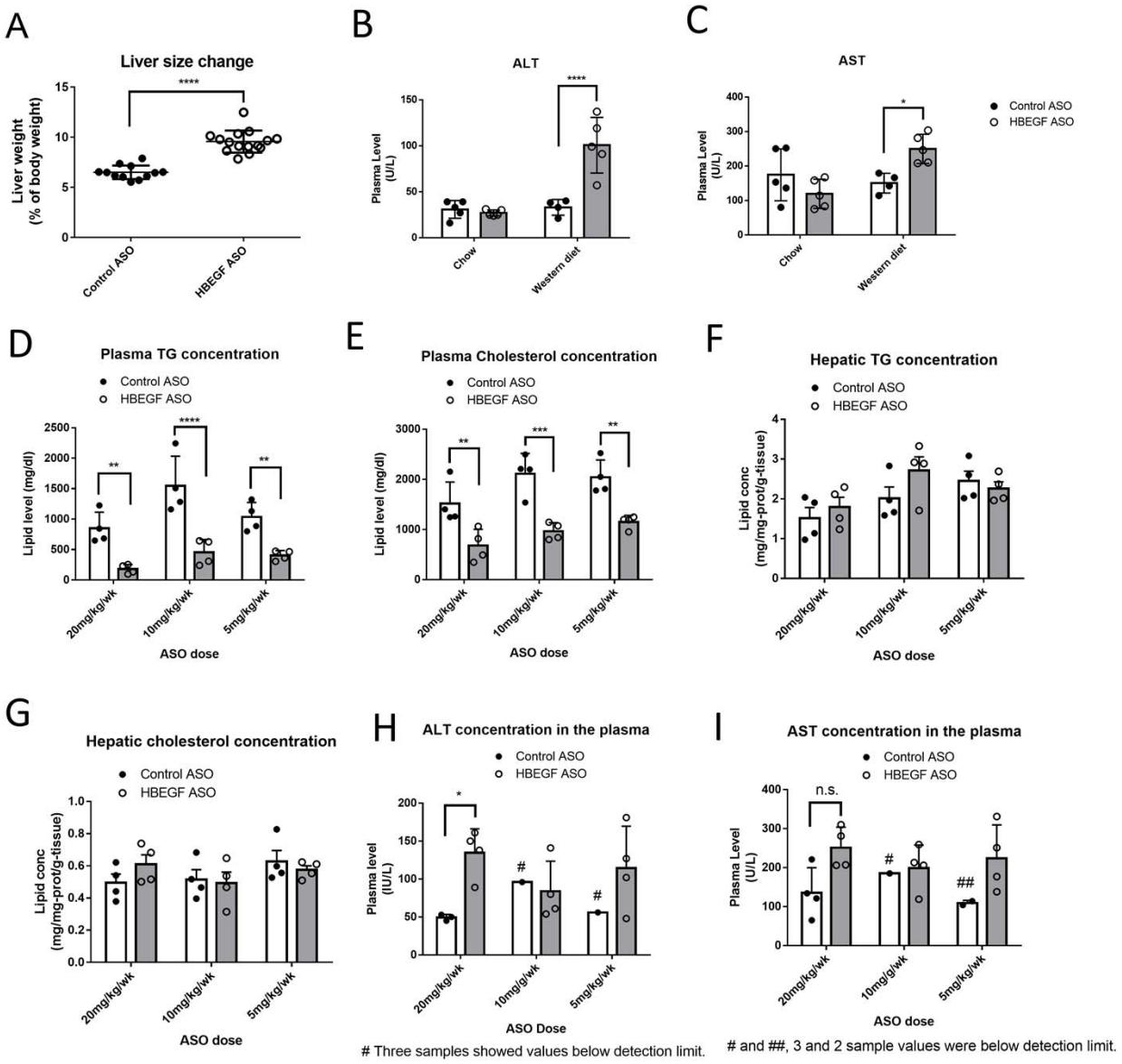
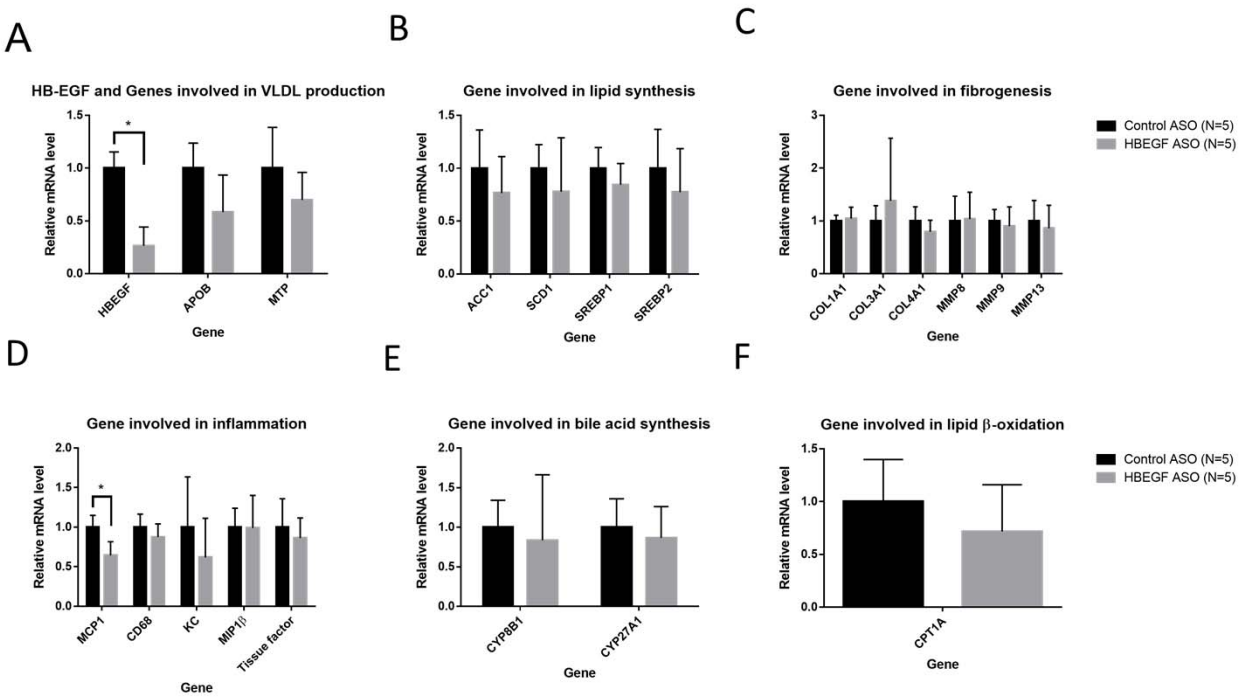


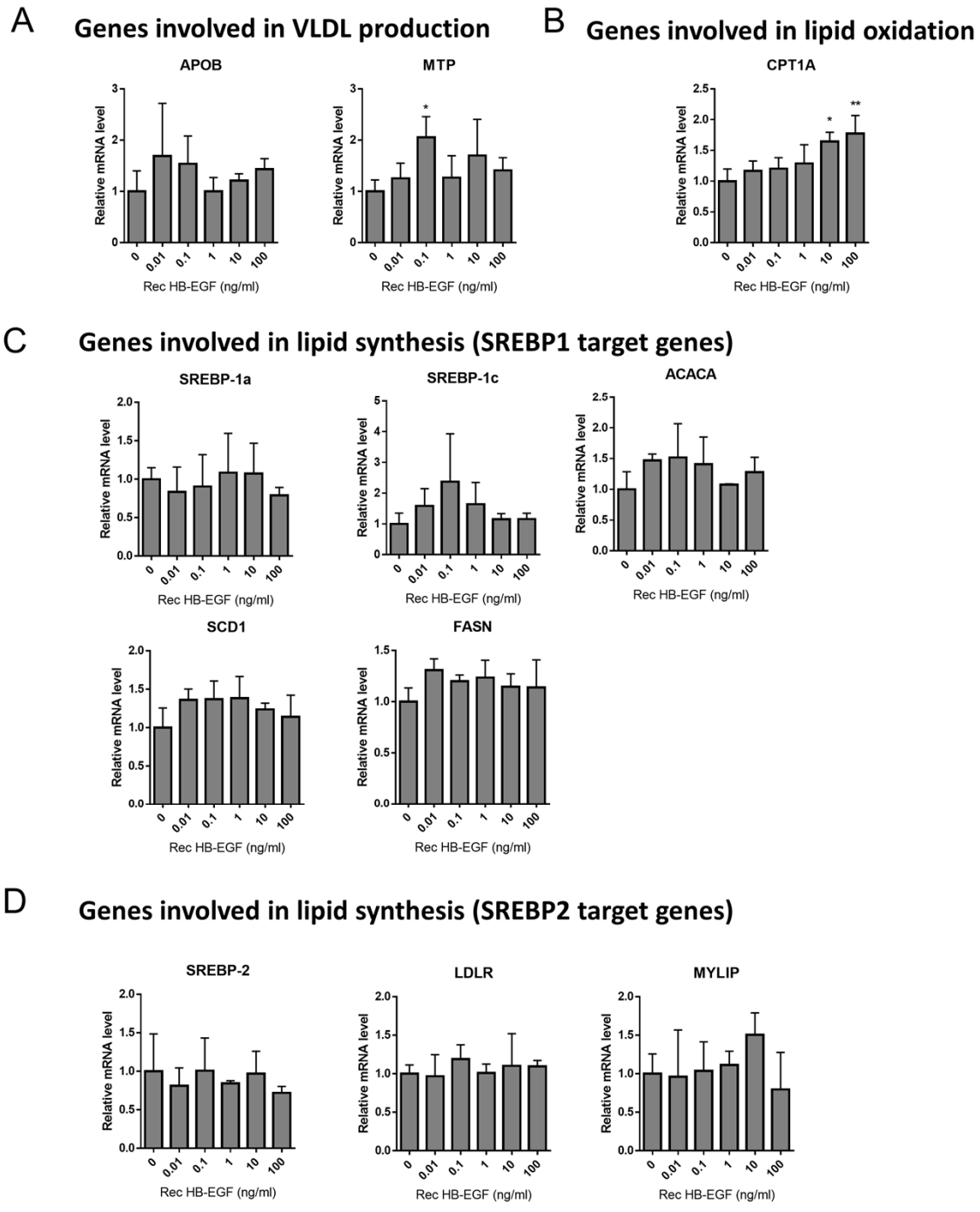
Figure 5. HB-EGF ASO administration affected haptic lipid concentration and functin with dose-dependently. (**A-C**) The LDLR deficient mice under Western diet were treated with control and HB-EGF ASOs for 12 weeks as described in Figure 1A. (**A**) The terminal liver weight was compared as the percent of the body weight. (**B-C**) The concentrations of the ALT and AST in the circulation were quantified for comparison. (**D-I**) The LDLR deficient mice under Western diet were treated with control and HB-EGF ASOs at doses of 20, 10, and 5 mg/kg/week for 16 weeks (N=4 per group). At the termination step, the plasma concentration of TG and cholesterol (**D, E**), and hepatic concentrations of the TG and cholesterol levels (**F, G**), and circulatory level of ALT and AST (**H, I**) were quantified. ** p<0.01, *** p<0.001, and n.s. means no significance.

Supplementary Figure 6



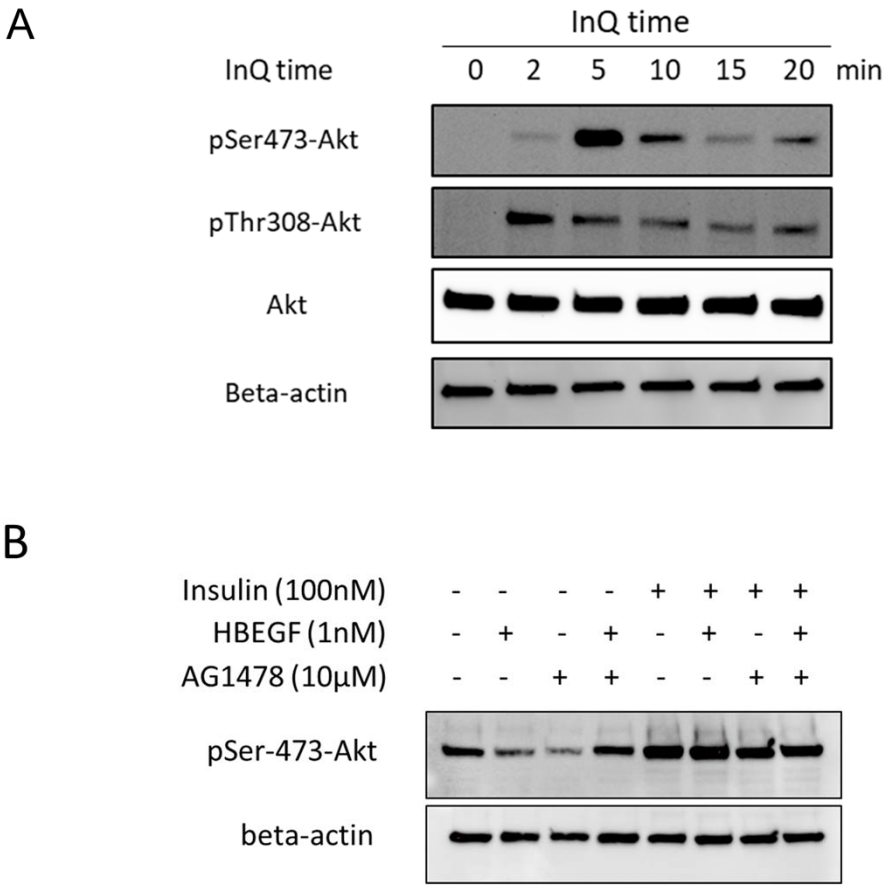
Supplemental Figure 6. Gene expression profile in the liver tissues. Liver tissues were isolated from the LDLR mice under Western diet cotreated with control and HB-EGF ASO administrations. Refer to main text **Figure 3** legend for mouse treatment scheme. The primer sequences for each gene qRT-PCR were described in **Supplementary Table 1.**

Supplementary Figure 7



Supplemental Figure 7. The gene expression profile in the HepG2 cells treated with recombinant HB-EGF. Confluent HepG2 cells were serum starved and treated with different doses of recombinant HB-EGF for 16 hours in DMEM supplemented with 0.1% BSA and 0.6 mM oleic acid (Three replicate for each treatment). The transcript levels of genes of interest in the cells were compared. The primer sequences were described in the Supplementary Table 1. * $p<0.05$.

Supplementary Figure 8



Supplemental Figure 8. The pretreatment of the recombinant HB-EGF did not affect the acute insulin signaling in the HepG2 cells. HepG2 cells with 100% confluency were serum starved in 1 day in DMEM media. (**A**) Next day, the cells were treated with recombinant insulin (100nM) for different time length. The cell lysates were prepared on the ice and the relative level of the total- and phosphorylated Akt (Ser473 and Thr308) was compared using the Western blotting analysis. (**B**) After one day of serum starvation as described above, the cells were pretreated with recombinant HB-EGF (1nM) with or without AG1478 (10μM) for perturbation of EGFR signaling for 16 hours. The cells were treated with recombinant insulin (100nM) for 5 min. The cell lysates were prepared on the ice, and the relative level of the phosphorylated Ser473-Akt was compared using the Western blotting analysis. The blots were reprobed with total Akt and/or beta-actin as a loading control. The information for the antibodies used for the Western blotting analysis described in Supplementary Table 2.