Supporting Information

Fig. S1. Effect of JTE-013 on TCA-induced activation of SphK2 in rat primary 1hepatocytes. Rat primary hepatocytes were pretreated with JTE-013 (10 μM) for 30 min, then treated with TCA (100 μM) for 30 min. Total cell lysates were prepared. The SphK1 and SphK2 activities were measured as described in "Methods". **P*<0.05, statistical significance relative to vehicle control, n=3. #*P*<0.05, statistical significance relative to TCA group, n=3.

Fig. S2. Effect of deletion of SphK2 or S1PR2 on hepatic lipid accumulation. A-B. Representative images of liver sections stained with hematoxylin and eosin (H&E) and Oil red O for (A) Wild type (WT) and SphK2$^{-/-}$ mice, (B) WT and S1PR2$^{-/-}$ mice. **C-D**. Mouse primary hepatocytes were isolated from Wild type, SphK2$^{-/-}$, or S1PR2$^{-/-}$ mice and plated on collagen-coated plates. The intracellular lipids were stained using Oil red O or Nile Red. Representative images are shown.

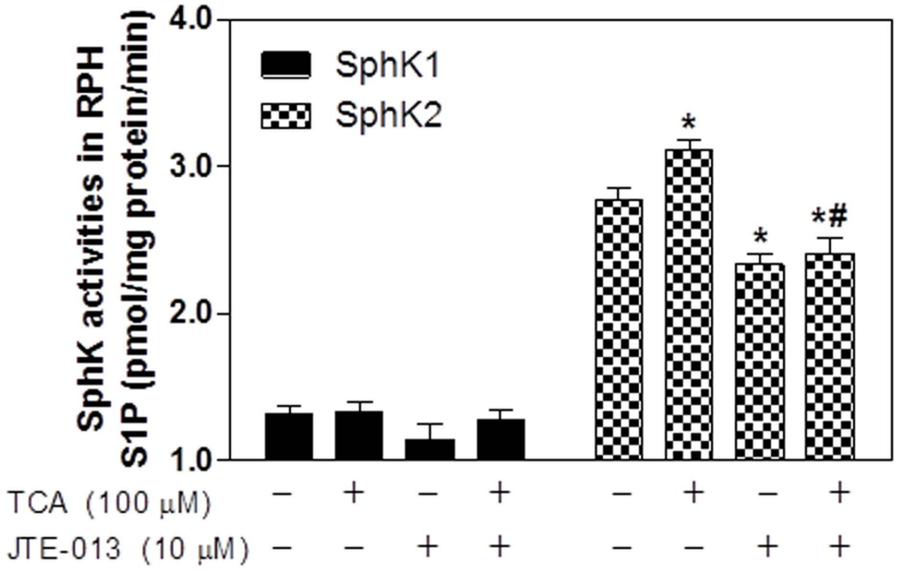
Fig. S3. Effect of SphK2$^{-/-}$ on mRNA levels of Hepatic Lipases. Total RNA was isolated from the livers of WT (Black) or SphK2$^{-/-}$ (Red) mice (male, 20-week old) under a normal chow diet (ND, solid bar) and high fat diet (HFD, checkered bar). The mRNA levels of hepatic lipase (HL) and hormone sensitive lipase (HSL) were determined using real time RT-PCR and normalized using β-actin. *P<0.05, **P<0.01, ***P<0.01, statistical significance relative to WT mice on ND, n=5-8; #P<0.05, statistical significance relative to SphK2$^{-/-}$ mice on ND.

Fig. S4. Quantitation of total cholesterol and triglycerides in livers of wild type and SphK2$^{-/-}$ mice on different diets. Wild type and SphK2$^{-/-}$ mice were fed a normal diet (ND), high fat diet (HFD) or high fat diet plus 1% cholic acid (HFD+CA) for 2 weeks. Animals were sacrificed, pieces of liver extracted by Folch extraction (Folch et al., 1957) and total cholesterol

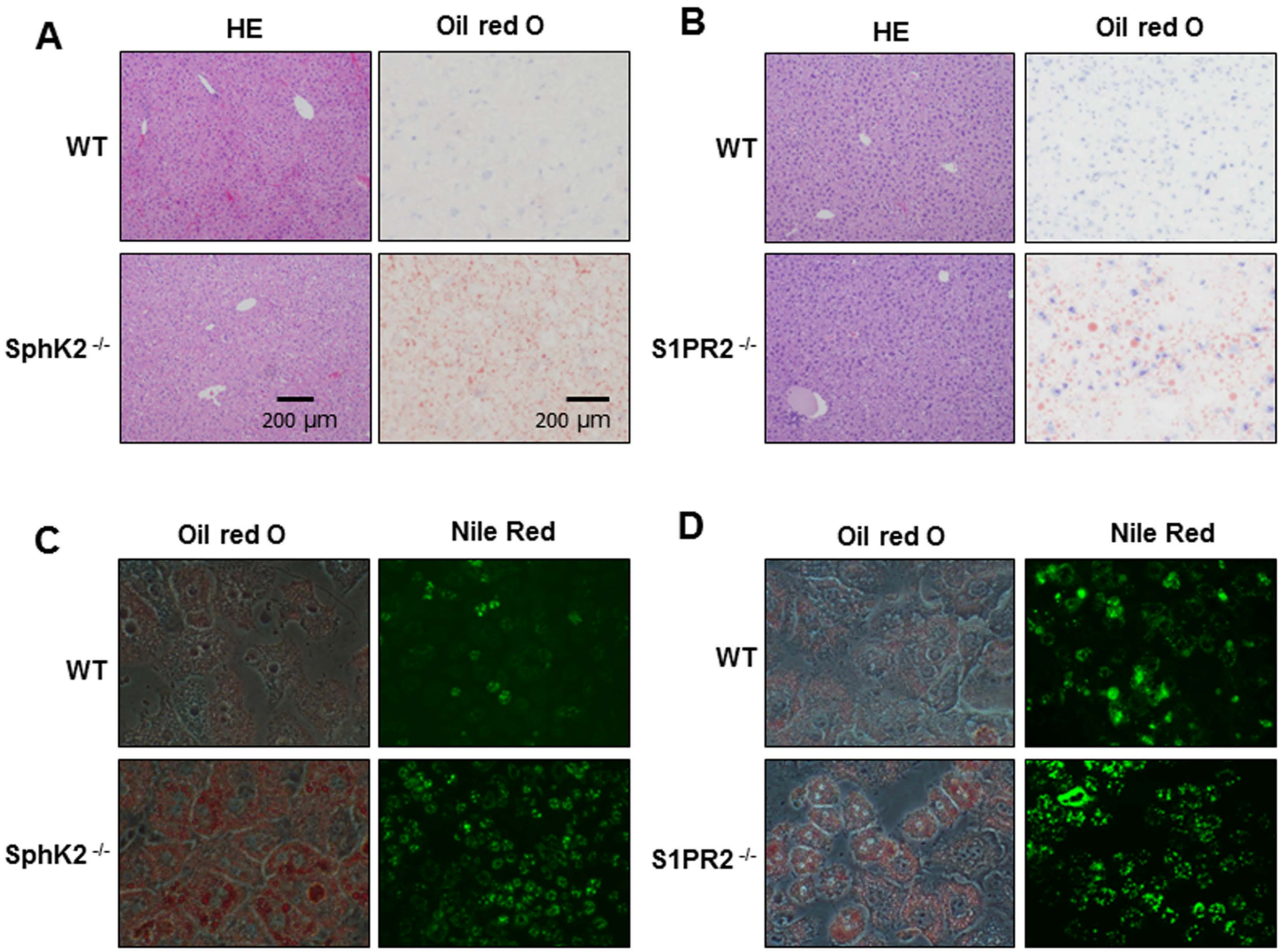
and triglycerides quantitated by Wako kit assays as described by the manufacturer**.** (A) Total cholesterol; (B) Triglycerides (TG). ***P*<0.05; ****P*<0.001 as compared to ND. #p<0.05 compared to wild type mouse on ND.

Fig. S5. Effect of SphK2$^{-/-}$ on mRNA levels of ApoB-100 and CPT-1α in hepatocytes. Total RNA was isolated from the primary hepatocytes of WT (Black) or SphK2$^{-/-}$ (Checked) mice. The mRNA levels of ApoB-100 and CPT-1α were determined using real-time RT-PCR and normalized using β-actin. *P<0.05, statistical significance relative to WT.

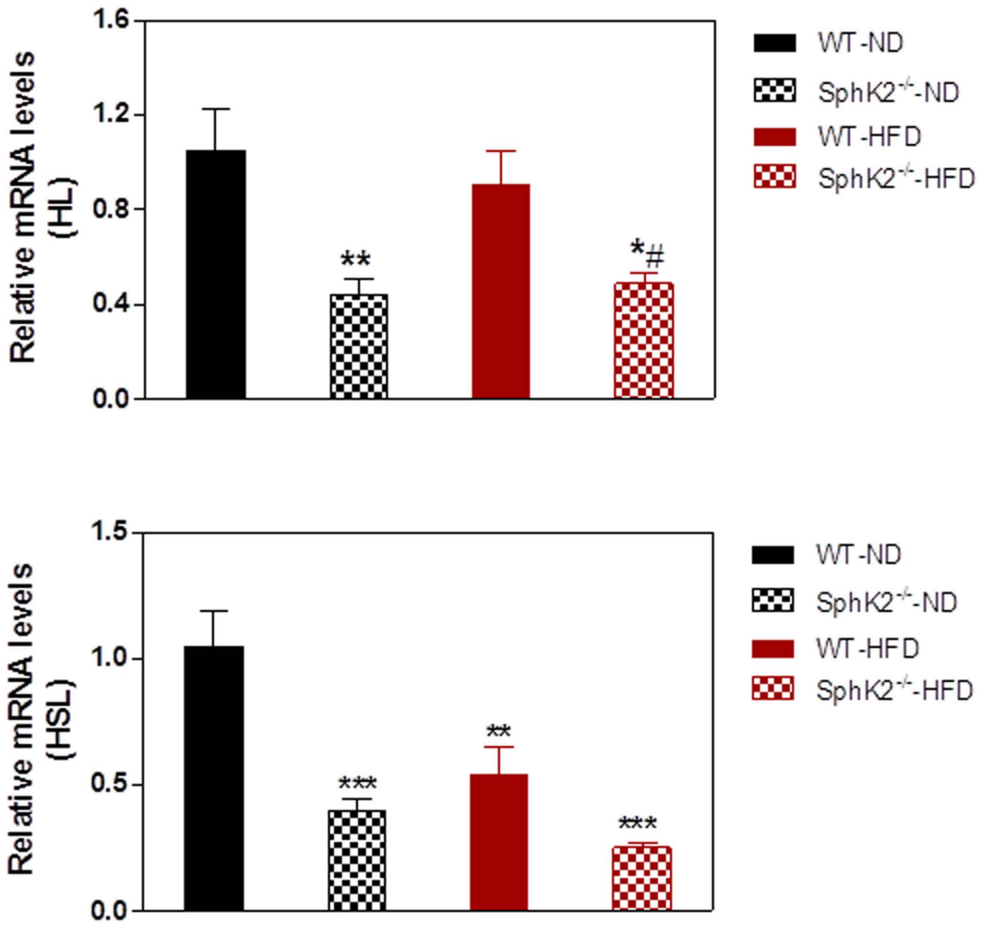
Online Figure S1



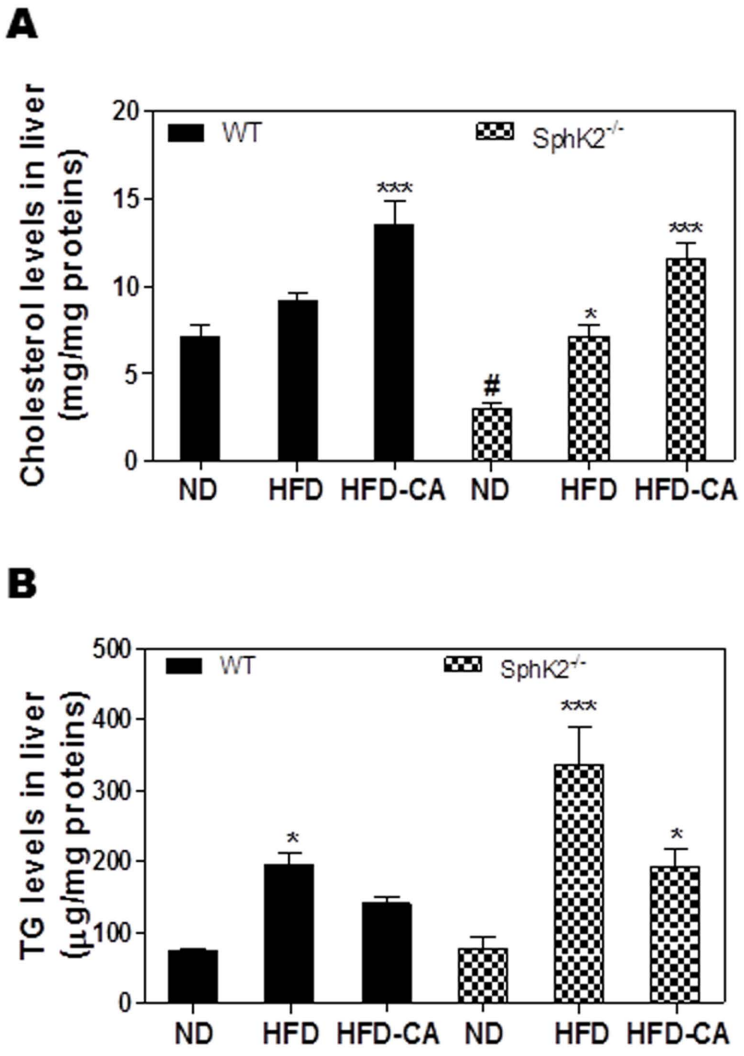
Online Figure S2



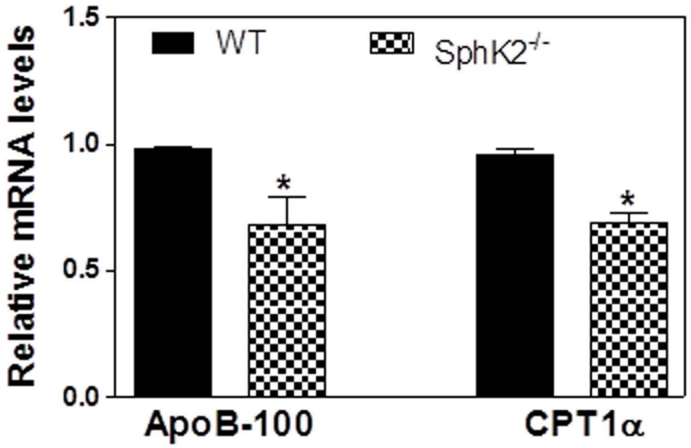
Online Figure S3



Online Figure S4



Online Figure S5



Online Table 1. Serum Analysis of Wild-type and SphK2$^{-/-}$ Mice in Different Diets

Diet	Mice	Glucose	Triglycerides	Chol.	HDL	LDL	ALT	AST	ALK
Normal	Wild-type	126±5	***25±2	28±1	**12±2	28±17	**13.6±4	69±21	<5
	SphK2$^{-/-}$	185±48	447±32	35±4	<5	<5	33±4	225±69	<5
High Fat	Wild Type	254±53	**34±5	***63±5	***45	**11	15±9	118±50	<5
	SphK2$^{-/-}$	199±37	420±72	33±3	<5	<5	32±7	250±85	<5
High Fat + Cholic Acid	Wild type	***99±25	***22±5	51±12	*11±2	**29±6	33±9	181±98	<5
	SphK2$^{-/-}$	283±49	364±28	28±4	<5	<5	31±4	382±149	<5

Statistical significance compared to SphK2$^{-/-}$ mice: *p<0.05; **p<0.01; ***p<0.001 (n=5-8).