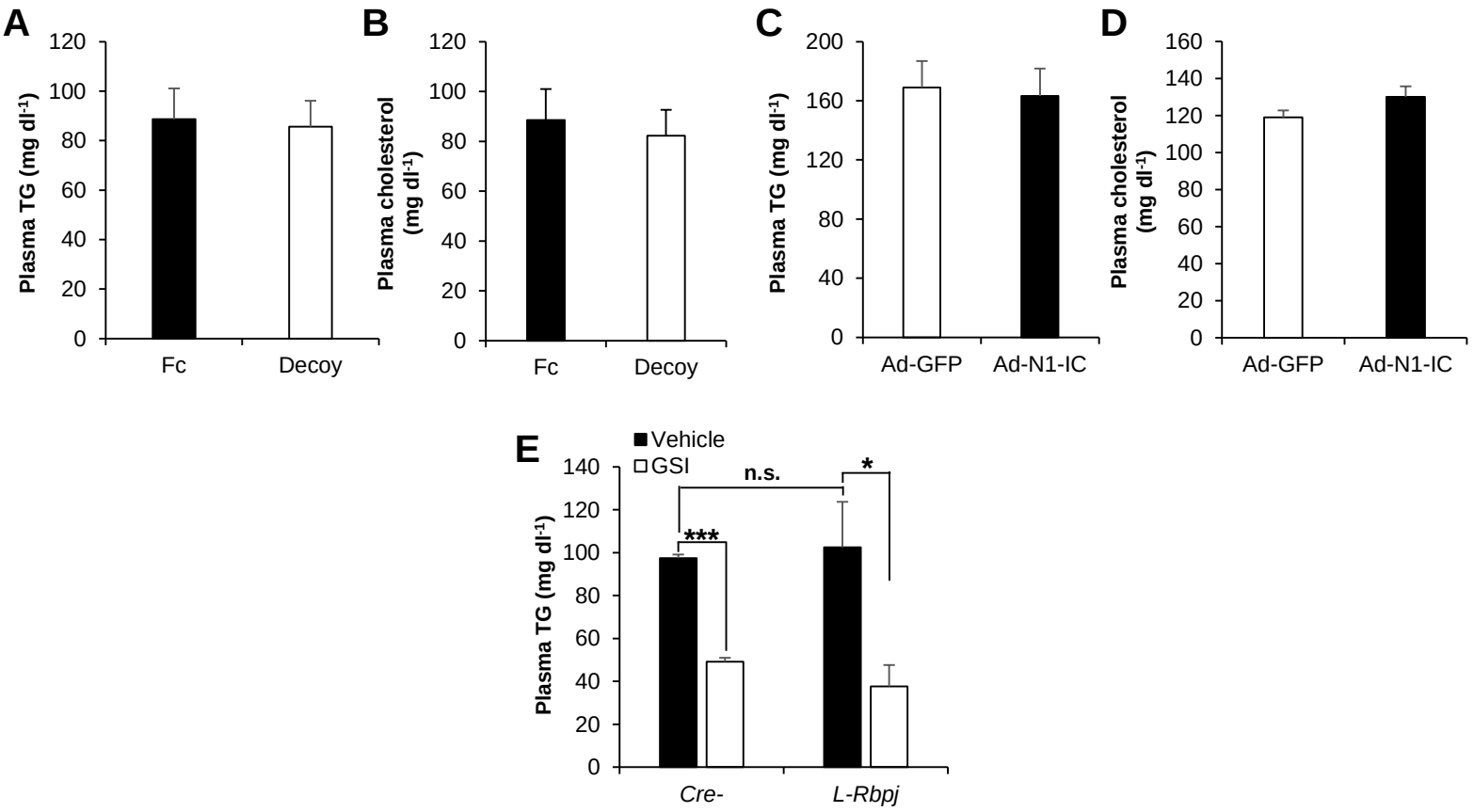

Figure S1, related to Fig 1. Hepatic Notch activity does not affect plasma lipids. (A-D) Plasma TG and cholesterol levels in C57BL/6 mice transduced with adenoviruses encoding either Ad-Fc control or Ad-Notch1 decoy (A and B) (n=5-6 per group) or Ad-GFP or constitutively-active Notch1 (Ad-N1-IC) (C and D) (n=5 per group). (E) Plasma TG levels in Cre- and *L-Rbpj* mice treated with vehicle or GSI (n=4 per group). **P* < 0.05, ****P* < 0.001 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.

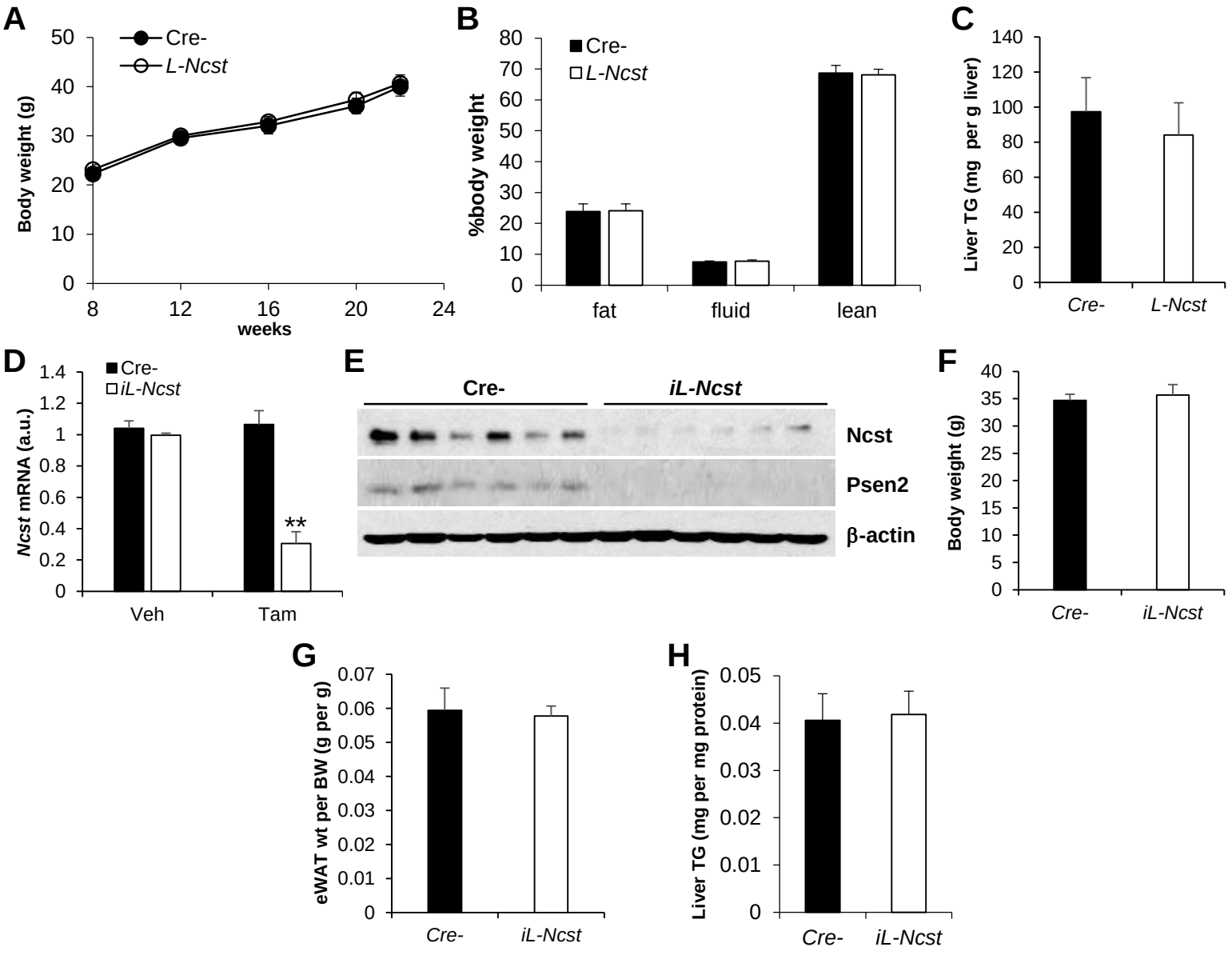

Figure S2, related to Fig 2. Hepatocyte-specific γ-secretase knockout mice do not have differences in body composition and liver TG. (A-C) Body weight (A), body composition (B) and liver TG (C) in Cre- or *L-Ncst* mice (n=6 per group). (D-F) Hepatic *Ncst* mRNA (D) and western blot for Ncst and Psen2 (E), and body weight (F), epididymal white adipose tissues (eWAT) weight (G), or liver TG (H) in tamoxifen-treated Cre- or *iL-Ncst* mice (n=6 per group). ***P* < 0.01 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.

Figure S3

A

Ionis No	Sequence	TSS ID	Position	Site ID	IC50	SVM Distance	Prediction	seqAloneModel_v2015-04-17_Score	seqAloneModel_v2015-04-17_Call
						In vitro Prediction		*In silico* Prediction	
806629	CAGAATAGACTTCCTC	I086121	14804	676848	< 0.22	1.72	Safe	0.79	SAFE
806498	ACTTATTCATCTCTCC	I066187	2336	676717	0.24	1.01	Safe	0.41	SAFE
806504	ACAGAAGGTATCCCGA	I066187	2461	676723	0.3	1.01	Safe	1.23	SAFE
806411	TTCTCGAGCCGCACGG	I066187	1122	676630	0.4	1.67	Safe	-1.14	TOXIC

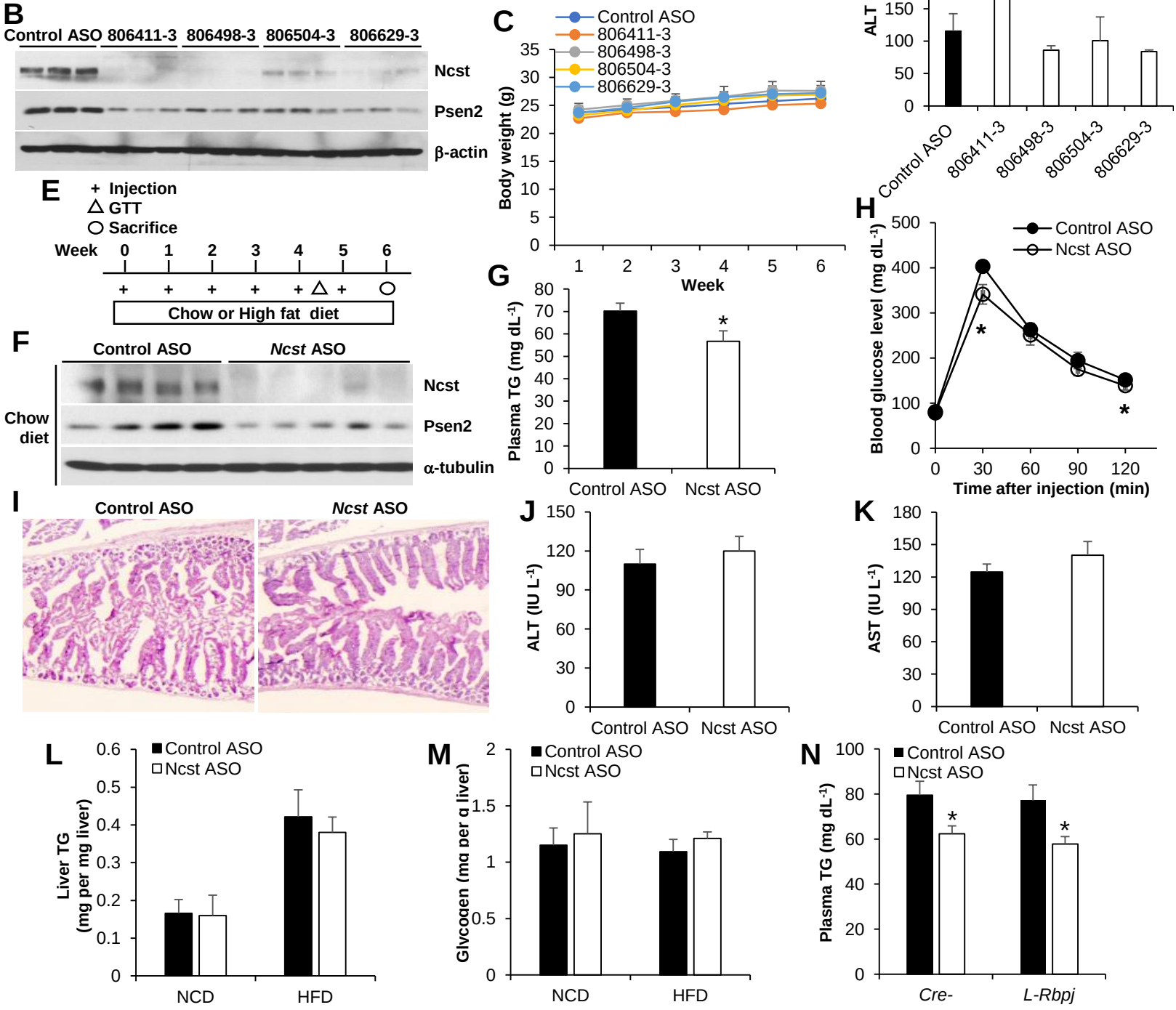

Figure S3, related to Fig 3. *Ncst* ASO reduces plasma TG, independent of liver Notch activity, without apparent toxicity. (A) Top leads for ASO directed against *Ncst*, based on *in vitro* efficacy and *in silico* predictions of toxicity. (B-D) Representative Western blots for liver Ncst and Psen2 (B), body weight curves during ASO administration (C) and plasma ALT (D) in C57BL/6 mice administered control and target ASOs. (E-M) Experimental outline (E), liver Ncst and Psen2 protein levels (F), plasma TG (G), glucose tolerance test (H), Periodic acid-Schiff (PAS) staining of small intestine (I), plasma ALT (J), AST (K) in chow-fed C57BL/6 mice, and liver TG (L) and glycogen (M) levels in chow- or HFD-fed C57BL/6 mice treated for 6 weeks with control or *Ncst* ASO (n=6-7 per group). (N) Plasma TG in Cre- and *L-Rbpj* mice treated for 6 weeks with control or Ncst ASO (n=6 per group). **P* < 0.05 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.

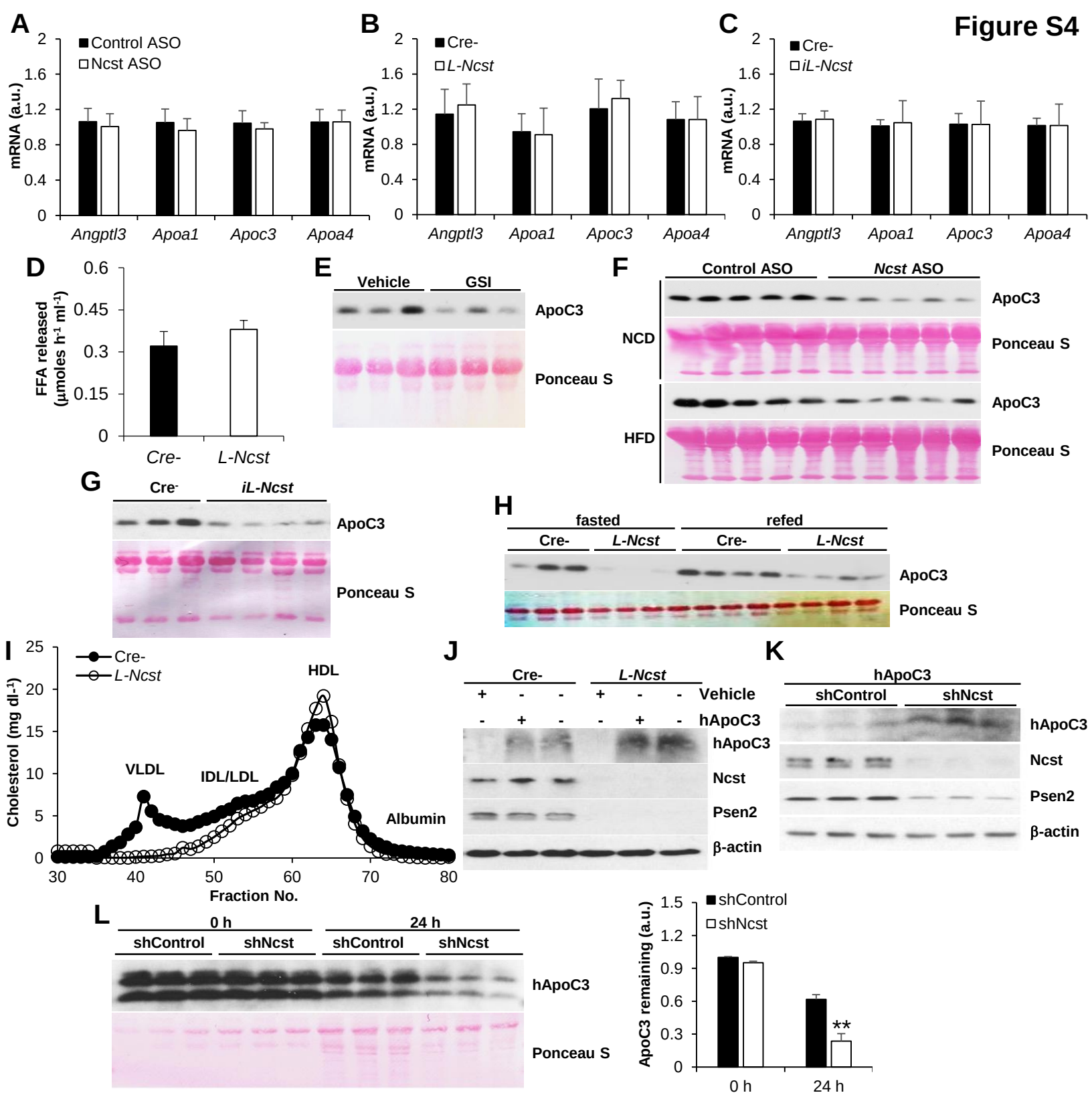

Figure S4, related to Fig 4. γ-secretase inhibition lowers plasma ApoC3 and induces the clearance of TRLs. (A-C) Liver gene expression in control- or *Ncst* ASO-treated (A), Cre- or *L-Ncst* (B) or tamoxifen-treated Cre- or *iL-Ncst* mice (C) (n=6-7 per group). (D) Lipoprotein lipase (LPL) activity in plasma from Cre- or *L-Ncst* mice (n=6-7 per group). (E-G) Representative Western blots of plasma ApoC3 in vehicle- or GSI-treated (E), control- or *Ncst* ASO-treated (F), tamoxifen-treated Cre- or *iL-Ncst* mice (G). (H) Western blots of ApoC3 in plasma from Cre- or *L-Ncst* mice, sacrificed after a 16 h fast followed by 4 h refeeding (n=6 per group). (I) Lipoprotein cholesterol profiles in plasma from Cre- or *L-Ncst* mice analyzed by FPLC (n=6 per group). (J and K) Western blots for intracellular human ApoC3 (hApoC3) in primary hepatocytes isolated from Cre- or *L-Ncst* mice (J) and shControl or shNcst-stable McA-RH7777 cells (K) incubated with hApoC3-containing plasma in the presence of MG-132 and chloroquine. (L) Western blot of starting (0 h) and remaining (24 h) hApoC3 in media of shControl or shNcst-stable McA-RH7777 cells (left), with quantitation relative to time 0 (right). $^{**}P < 0.01$ as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.

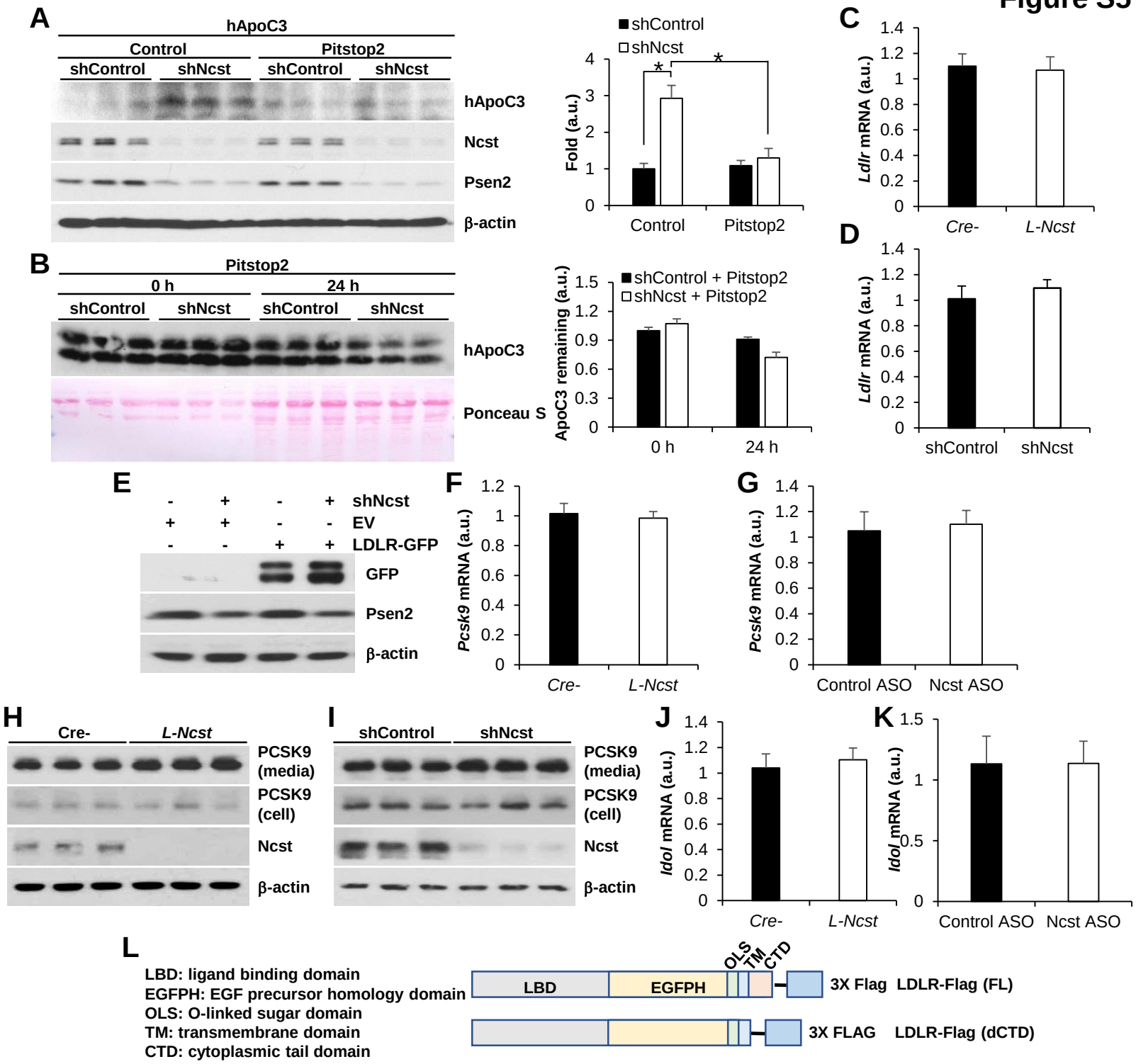

Figure S5, related to Fig 5. γ-secretase inhibition induces ApoC3 uptake and stabilizes LDLR protein, but does not affect *Pcsk9* or *Idol*. (A) Western blots for intracellular hApoC3 levels in shControl or shNcst-stable McA-RH7777 cells, incubated with hApoC3-containing plasma in the presence of MG-132 and chloroquine, with or without Pitstop2, with quantitation of intracellular hApoc3/β-actin. (B) Western blot of hApoC3 in media of McA-RH7777 cell with stable expression of shControl or shNcst, in the presence of Pitstop2. (C and D) *Ldlr* mRNA expression in livers from Cre- or *L-Ncst* mice (C) (n=6 per group) and in McA-RH7777 cells expressing shControl or shNcst (D) (n=4 per group). (E) Western blot of exogenous LDLR with either C-terminal GFP-tags in shControl or shNcst-stable McA-RH7777 cells. (F and G) *Pcsk9* mRNA expression in livers from Cre- or *L-Ncst* mice (F) (n=6 per group) and control- or *Ncst* ASO-treated mice (G) (n=6-7 per group). (H and I) Western blot of PCSK9 in media or cells from primary hepatocytes isolated from either Cre- or *L-Ncst* mice (H) and McA-RH7777 cells expressing shControl or shNcst (I). (J and K) *Idol* mRNA expression in livers from Cre- or *L-Ncst* mice (J) (n=6 per group) or control- or *Ncst* ASO-treated mice (K) (n=6-7 per group). (L) Schematic of LDLR with (full-length, FL) or without (dCTD) the C-terminal domain. *$P < 0.05$ as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.

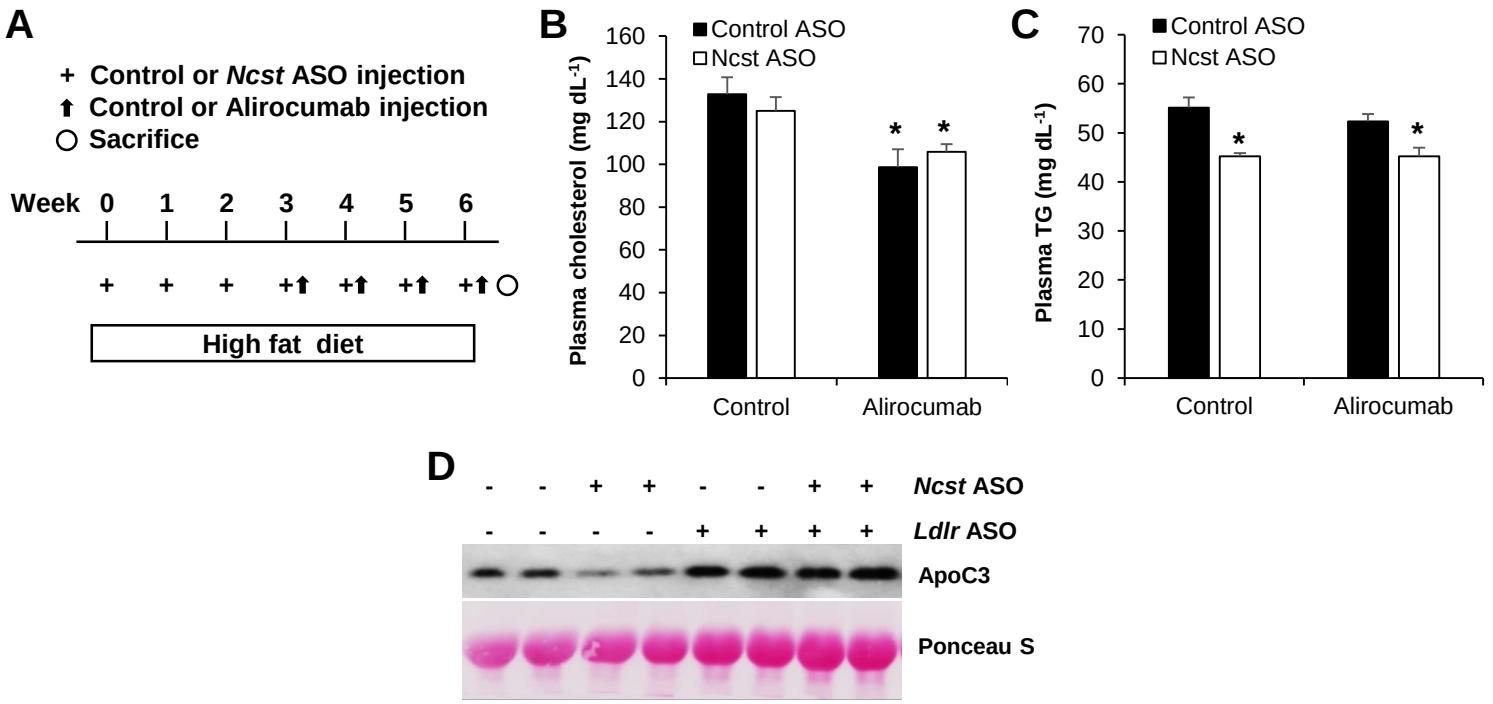

Figure S6, related to Fig 6. *Ncst* ASO reduces plasma TG independent of PCSK9i and increases plasma ApoC3 levels. (A-C) Experimental outline (A), plasma cholesterol (B) and TG (C) in HFD-fed C57BL/6 mice treated for 6 weeks with control or *Ncst* ASO, with or without alirocumab co-treatment (n=7 per group). (D) Plasma ApoC3 levels in mice injected with control, *Ncst* and/or *Ldlr* ASO. **P* < 0.05 as compared to the indicated control by two-way ANOVA. All data are shown as the means ± s.e.m.