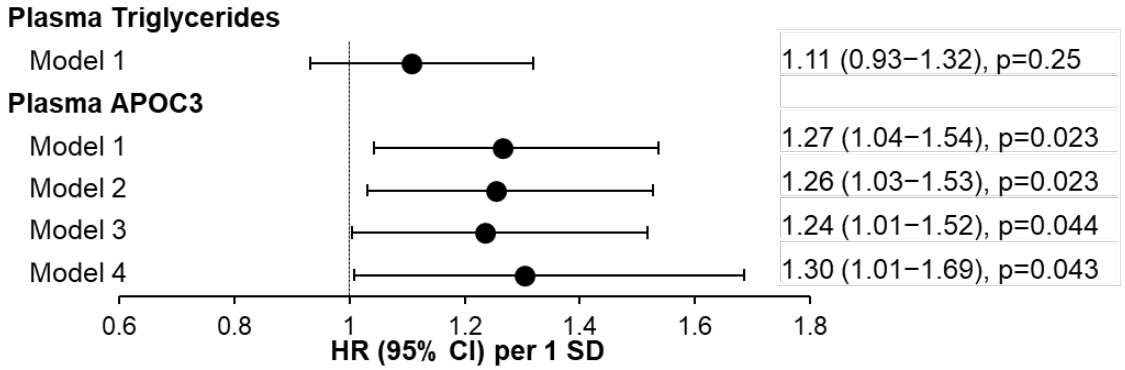
Extended Data Figures 1-10

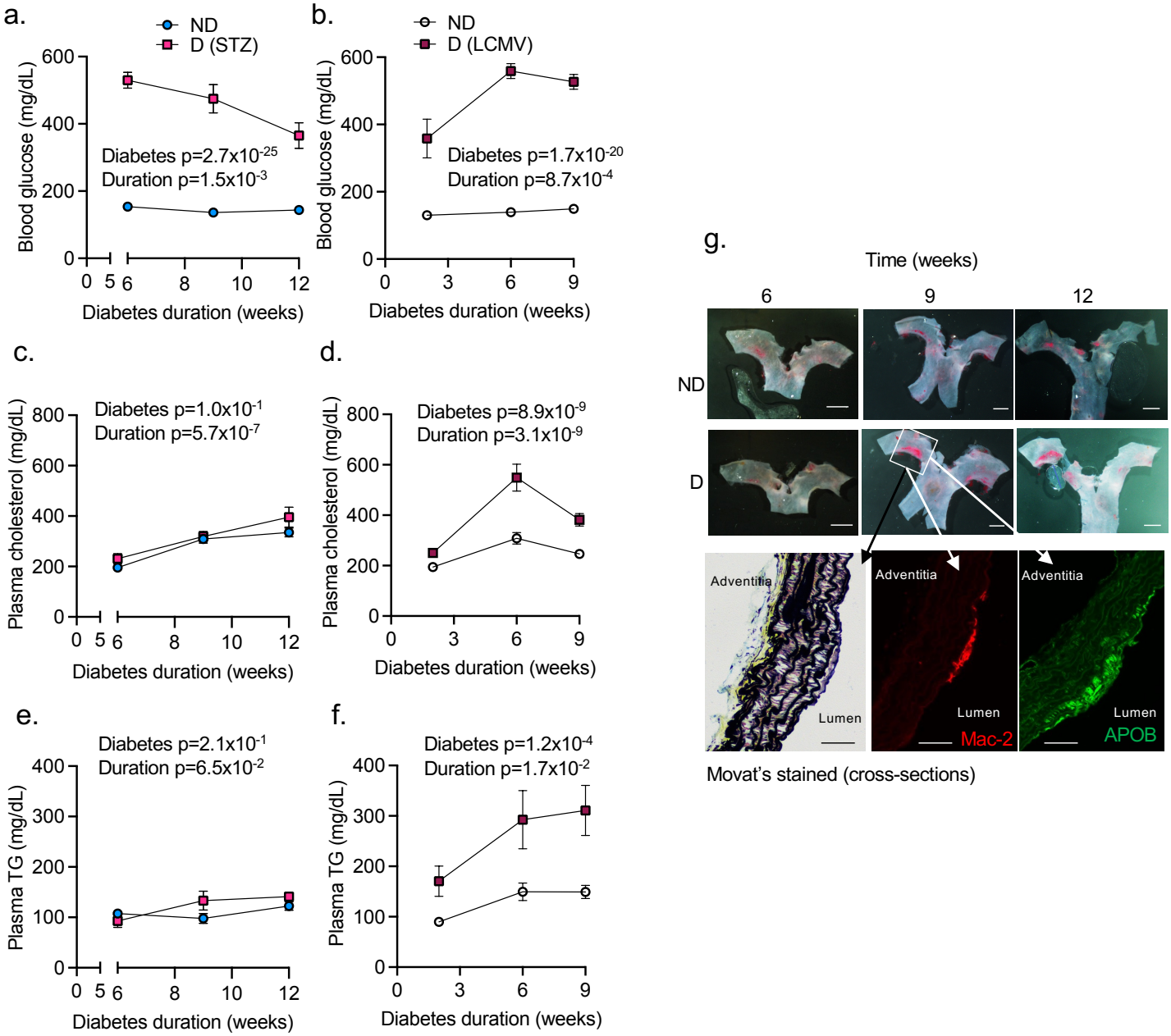
a.

Variable	All	Normal FG	Impaired FG	Diabetes
N	5,743	4,187	822	724
Age (years)	63 ± 10	62 ± 10	65 ± 10	66 ± 9
Non-Hispanic Whites	2,148 (37%)	1,765 (42%)	253 (31%)	130 (18%)
Blacks	1,659 (29%)	1,117 (27%)	251 (30%)	291 (39%)
Hispanics	1,257 (22%)	829 (20%)	202 (24%)	226 (31%)
Chinese	702 (12%)	488 (12%)	123 (15%)	91 (12%)
Women	3,004 (52%)	2,294 (55%)	366 (44%)	34 (47%)
Past tobacco use	2,130 (37%)	1,540 (37%)	306 (37%)	284 (39%)
Current tobacco use	725 (13%)	540 (13%)	98 (12%)	87 (12%)
BMI (kg/m^2)	28.3 ± 5.5	27.6 ± 5.2	29.9 ± 5.5	30.6 ± 5.8
Antihypertensives	2,182 (38%)	1,317 (32%)	386 (47%)	479 (65%)
Systolic Blood Pressure (mmHg)	127 ± 22	125 ± 21	132 ± 21	134 ± 22
Diastolic Blood Pressure (mmHg)	72 ± 10	72 ± 10	74 ± 11	72 ± 10
Fasting glucose (mmol/L)	5.44 ± 1.72	4.80 ± 0.39	5.98 ± 0.39	8.39 ± 3.09
Triglycerides (mmol/L)	1.45 ± 0.80	1.37 ± 0.75	1.61 ± 0.88	1.70 ± 0.91
Total cholesterol (mmol/L)	5.02 ± 0.92	5.05 ± 0.90	5.03 ± 0.89	4.84 ± 0.98
HDL-cholesterol (mmol/L)	1.32 ± 0.39	1.36 ± 0.40	1.23 ± 0.33	1.19 ± 0.32
LDL-cholesterol (mmol/L)	3.03 ± 0.82	3.05 ± 0.81	3.07 ± 0.80	2.88 ± 0.86
eGFR (mL/min/1.73 m^2)	89 ± 17	89 ± 16	88 ± 17	89 ± 21

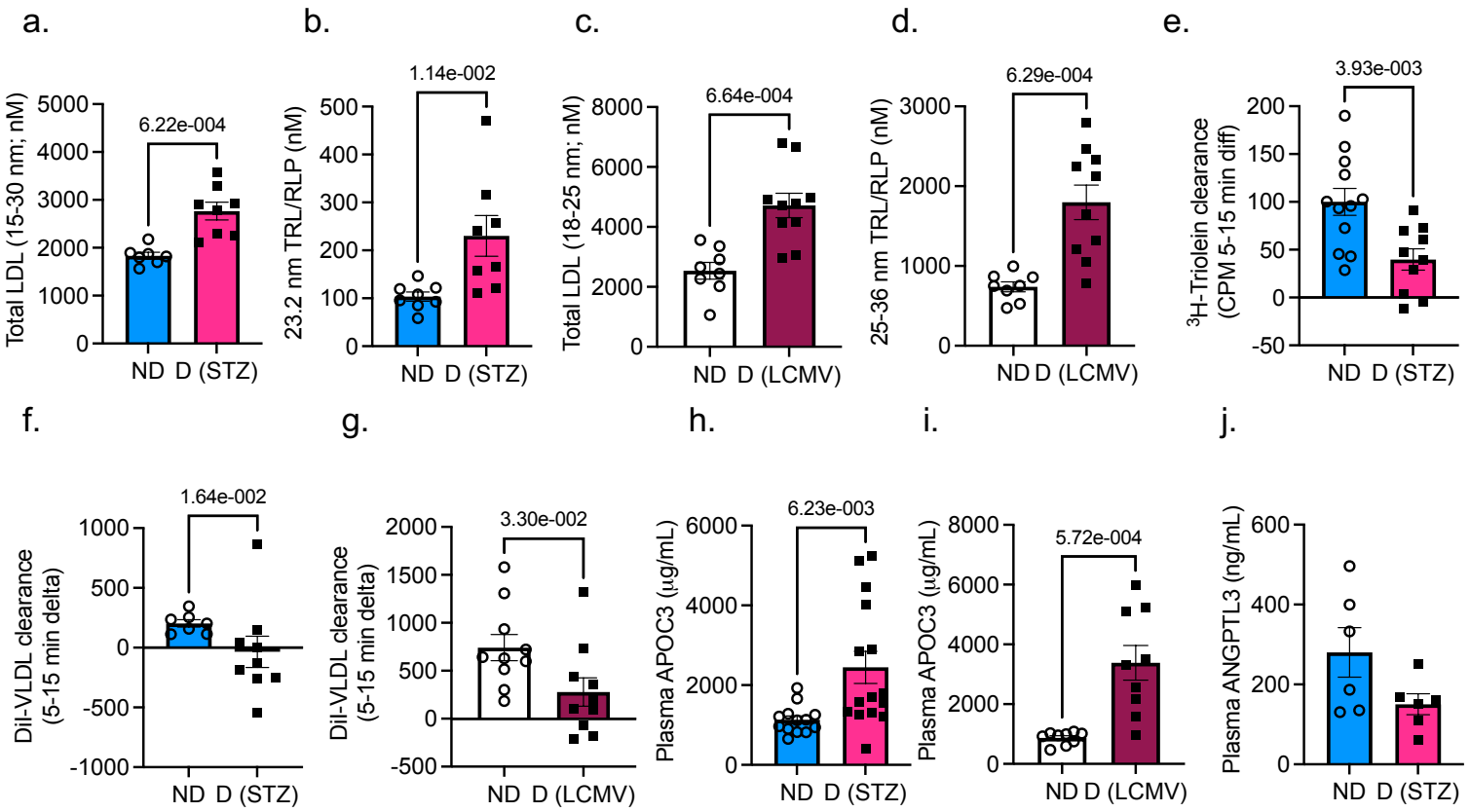
b.



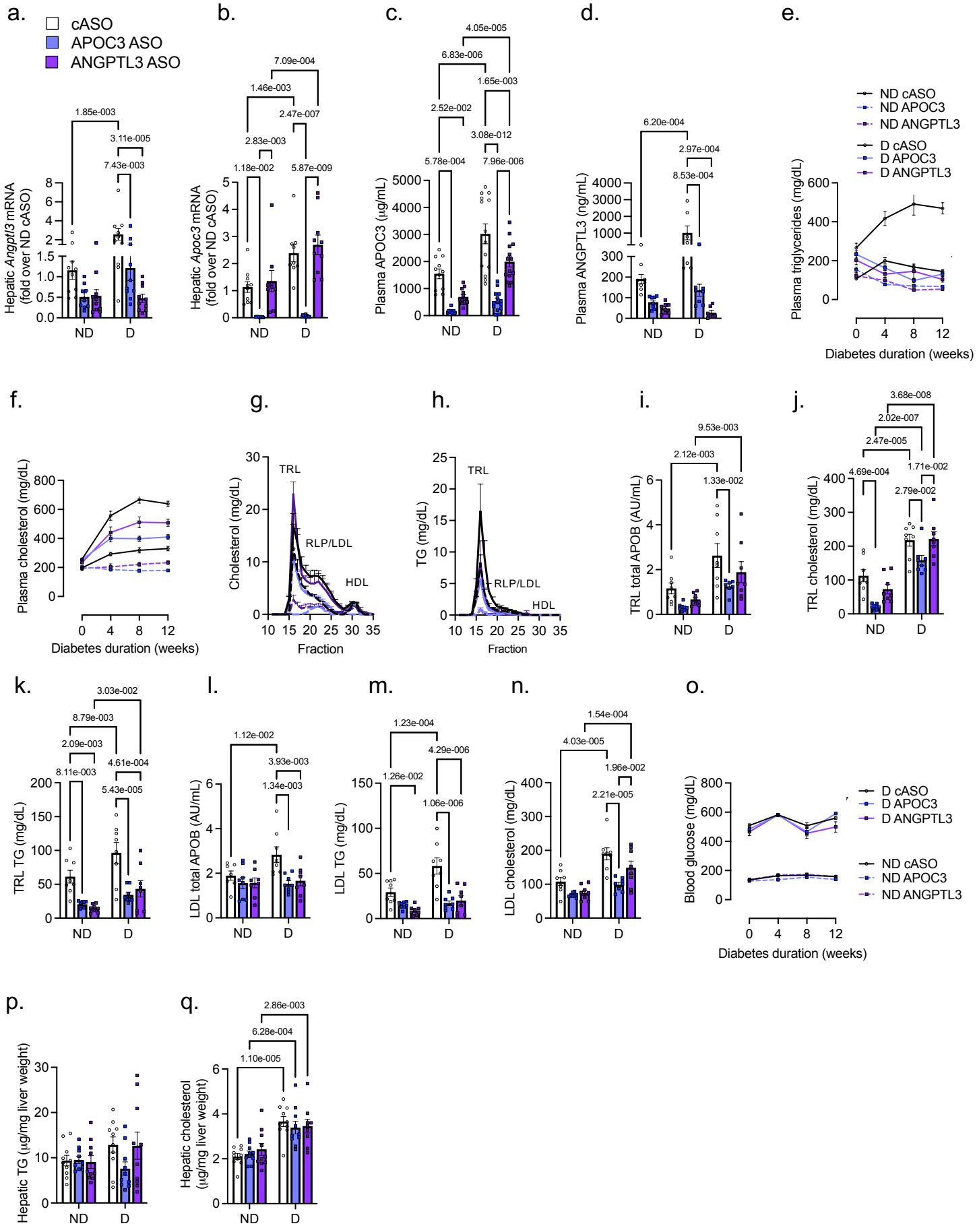
Extended Data Figure 1. Plasma APOC3 levels predict incident CVD events in individuals with type 2 diabetes. **a**. Association between total plasma APOC3 and incident major adverse cardiovascular events (MACE) was tested in baseline samples of 724 participants of the Multiethnic Study of Atherosclerosis (MESA) community-based longitudinal cohort who had diabetes at baseline. MACE was defined as myocardial infarction, resuscitated cardiac arrest or stroke. All MESA participants were free of cardiovascular disease at the enrollment. Participants with plasma TG of 500 mg/dL or higher were excluded from the analyses to account for excess APOC3 levels due to non-fasting condition or primary hypertriglyceridemia. A total of 153 MACE events occurred after a median 7.8 years (median censor 12.5 years). Cox proportional hazard regression models were adjusted for age, sex and race/ethnicity (Model 1), then further adjusted for use of antihypertensive medications, systolic blood pressure and tobacco use (Model 2), then Model 2 variables and plasma LDL-cholesterol and HDL-cholesterol (Model 3), and Model 2 variables and plasma triglycerides (Model 4). **b**. Baseline clinical and demographic characteristics of MESA participants by fasting glucose (FG) status. Data are means ± SD or counts (%). eGFR, estimated glomerular filtration rate.



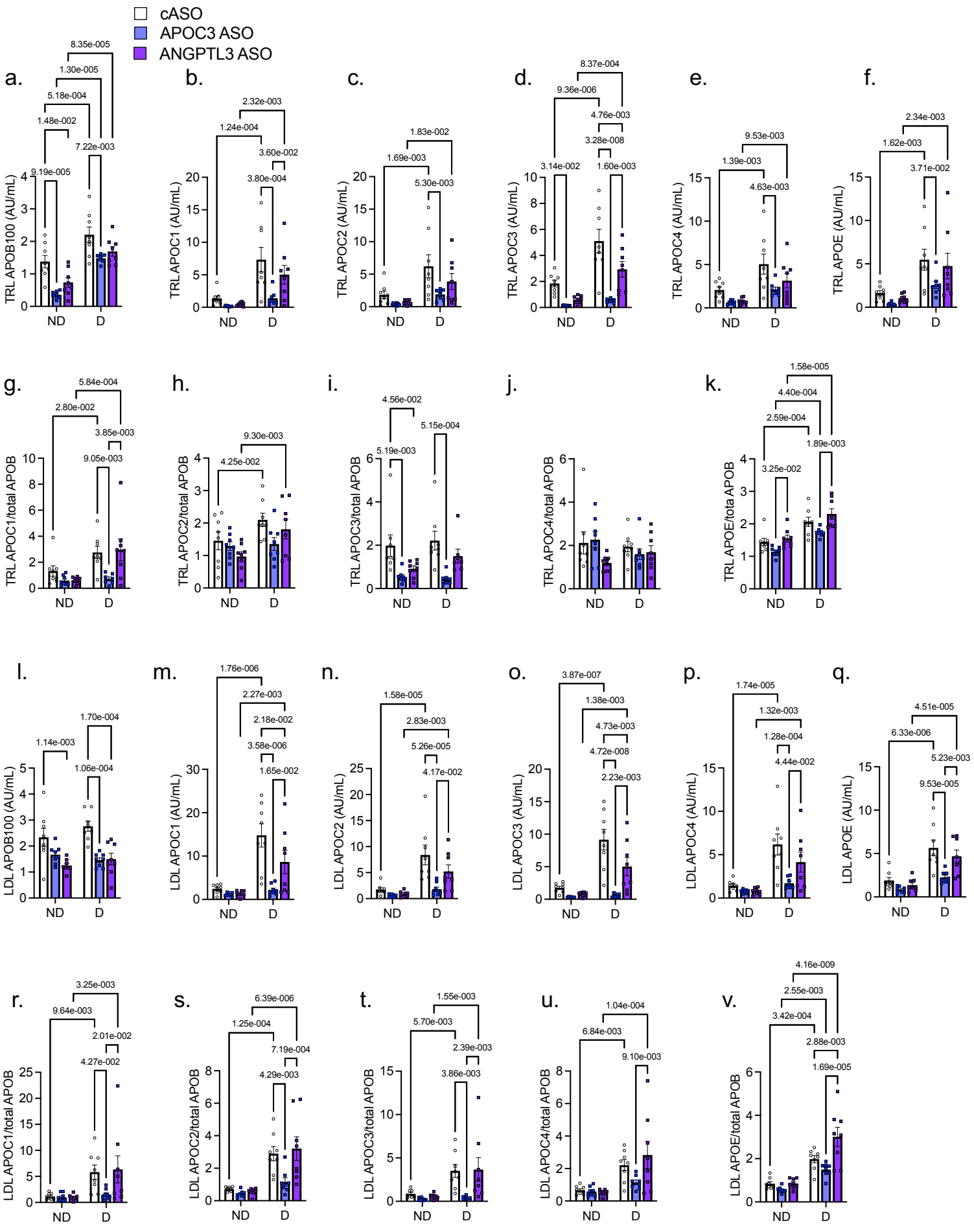
Extended Data Figure 2. Characterization of the mouse diabetes models. Diabetes was induced using two different approaches in female *Ldlr*$^{-/-}$ mice. Low-dose streptozotocin (STZ; 50 mg/kg for five days, beta-cell toxin; **a, c, e**) or injection of lymphocytic choriomeningitis virus (LCMV) in transgenic mice expressing the LCMV GP transgene under control of the insulin promoter, resulting in cytotoxic T cell-mediated destruction of the pancreatic beta-cells following LCMV injection (a model mimicking autoimmune diabetes) (**b, d, f**). After diabetes onset, the diabetic (D) and non-diabetic (ND) mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 2-12 weeks. **a.** Blood glucose in the STZ model. **b**. Blood glucose in the autoimmune LCMV model. **c**. Plasma cholesterol in the STZ model over the 12-week study. **d**. Plasma cholesterol in the autoimmune LCMV model during the 9-week study. **e**. Plasma triglycerides in the STZ model over the 12-week study. **f**. Plasma triglycerides in the autoimmune LCMV model over the 9-week study. **g**. Example of Sudan IV-stained aortic arches with corresponding cross-sectional analysis using Movat's pentachrome, Mac-2, and APOB immunostaining from the STZ model of diabetes. Scale bar is 1 mm and 100 μm for *en face* and cross sectioned aortas, respectively. Data are expressed as mean ± SEM. Statistical analyses were performed by two-way ANOVA with the overall statistical significance shown in the graphs. See also Original Data Supplement.



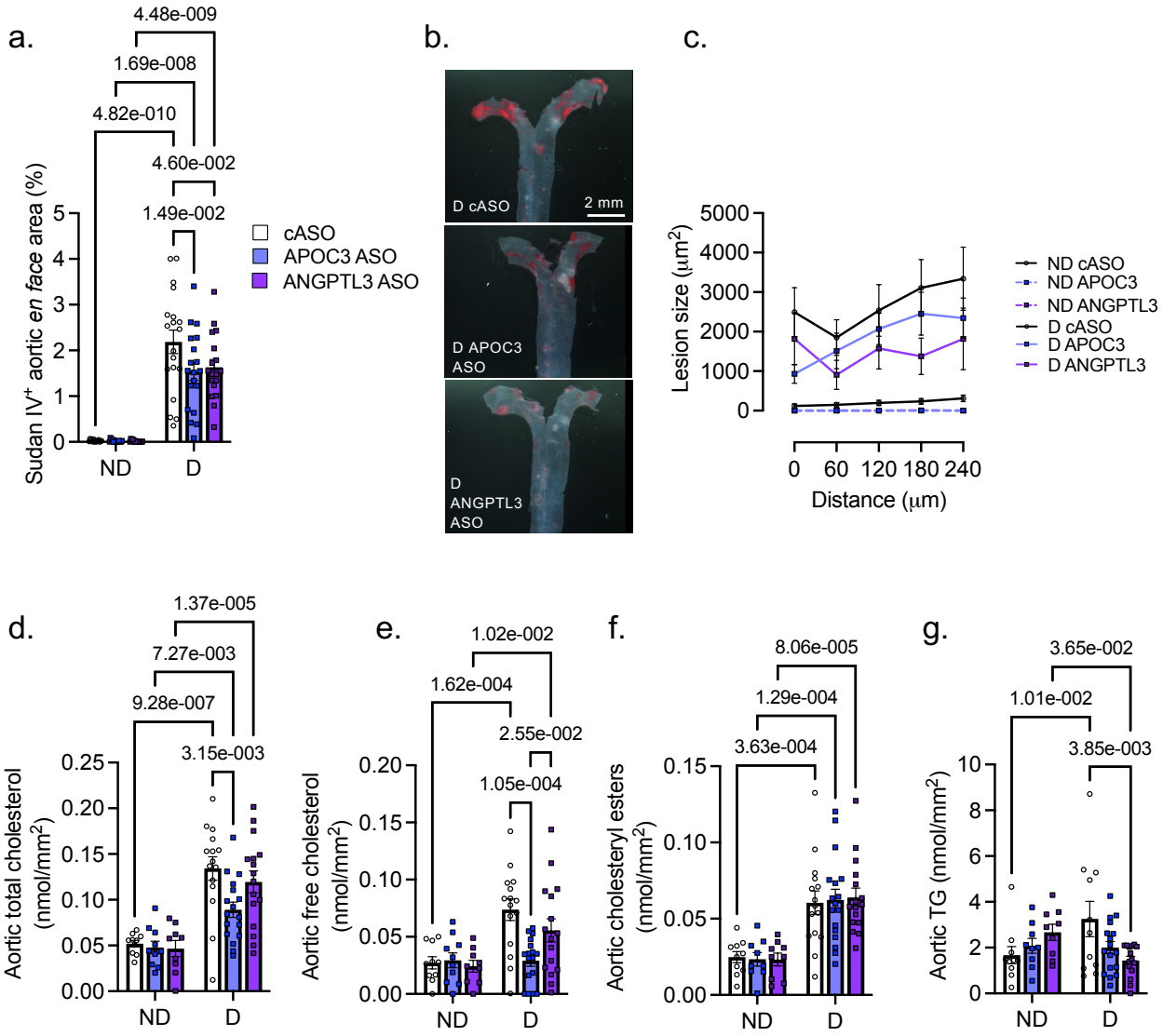
Extended Data Figure 3. Both mouse models of diabetes exhibit increased plasma concentrations of TRLs/RLPs and slowed TRL clearance rates. Concentrations and sizes of low-density lipoproteins (LDL; density 1.08-1.019 g/mL) and triglyceride-rich lipoproteins and their remnants (TRL; density <1.019 g/mL after removal of large chylomicrons) were measured by calibrated differential ion mobility analysis (DMA) in each density fraction. **a**. Total LDL concentration of particles ranging from 15-30 nm in the STZ model. **b**. TRL/RLP (23 nm) particle concentration in the STZ model. **c**. Total LDL concentration of particles ranging from 18-25 nm in the LCMV model. **d**. TRL/RLP (25-36 nm) particle concentration in the autoimmune LCMV diabetes model. **e**. Clearance of ^{3}H-triolein-labeled chylomicrons (isolated from glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 [GPIHBP1] knock-out mice). **f**. Clearance of DiI-labeled VLDL (isolated from fasted high-fat-fed *Ldlr*$^{-/-}$ mice). **g**. Clearance of DiI-labeled VLDL (isolated from fasted high-fat-fed *Ldlr*$^{-/-}$ mice). **h**. Plasma APOC3 in the STZ model. **i**. Plasma APOC3 in the LCMV diabetes model. **j**. Plasma ANGPTL3 in the STZ model. The lack of increase of plasma ANGPTL3 in this model versus the LCMV model of diabetes (Extended Data Fig. 4d) is likely due to the lack of severe hyperlipidemia in the STZ model (Extended Data Fig. 2c-f). Data are expressed as mean ± SEM; unpaired t-test (b-e, g-i) or Mann-Whitney test (a, f, j). See also Original Data Supplement.


a.
cASO
APOC3 ASO
ANGPTL3 ASO
Hepatic Angptl3 mRNA (fold over ND cASO)
1.85e-003
3.11e-005
7.43e-003
ND
D
b.
Hepatic Apoc3 mRNA (fold over ND cASO)
7.09e-004
1.46e-003
2.47e-007
2.83e-003
1.18e-002
5.87e-009
c.
Plasma APOC3 (µg/mL)
4.05e-005
6.83e-006
1.65e-003
2.52e-002
3.08e-012
5.78e-004
7.96e-006
d.
Plasma ANGPTL3 (ng/mL)
6.20e-004
2.97e-004
8.53e-004
e.
ND cASO
ND APOC3
ND ANGPTL3
D cASO
D APOC3
D ANGPTL3
Plasma triglycerides (mg/dL)
Diabetes duration (weeks)
f.
Plasma cholesterol (mg/dL)
Diabetes duration (weeks)
g.
TRL
RLP/LDL
HDL
Cholesterol (mg/dL)
Fraction
h.
TRL
RLP/LDL
HDL
TG (mg/dL)
Fraction
i.
TRL total APOB (AU/mL)
9.53e-003
2.12e-003
1.33e-002
j.
TRL cholesterol (mg/dL)
3.68e-008
2.02e-007
2.47e-005
1.71e-002
4.69e-004
2.79e-002
k.
TRL TG (mg/dL)
3.03e-002
8.79e-003
2.09e-003
4.61e-004
8.11e-003
5.43e-005
l.
LDL total APOB (AU/mL)
1.12e-002
3.93e-003
1.34e-003
m.
LDL TG (mg/dL)
1.23e-004
4.29e-006
1.26e-002
1.06e-006
n.
LDL cholesterol (mg/dL)
1.54e-004
4.03e-005
1.96e-002
2.21e-005
o.
Blood glucose (mg/dL)
D cASO
D APOC3
D ANGPTL3
ND cASO
ND APOC3
ND ANGPTL3
Diabetes duration (weeks)
p.
Hepatic TG (µg/mg liver weight)
q.
Hepatic cholesterol (µg/mg liver weight)
2.86e-003
6.28e-004
1.10e-005

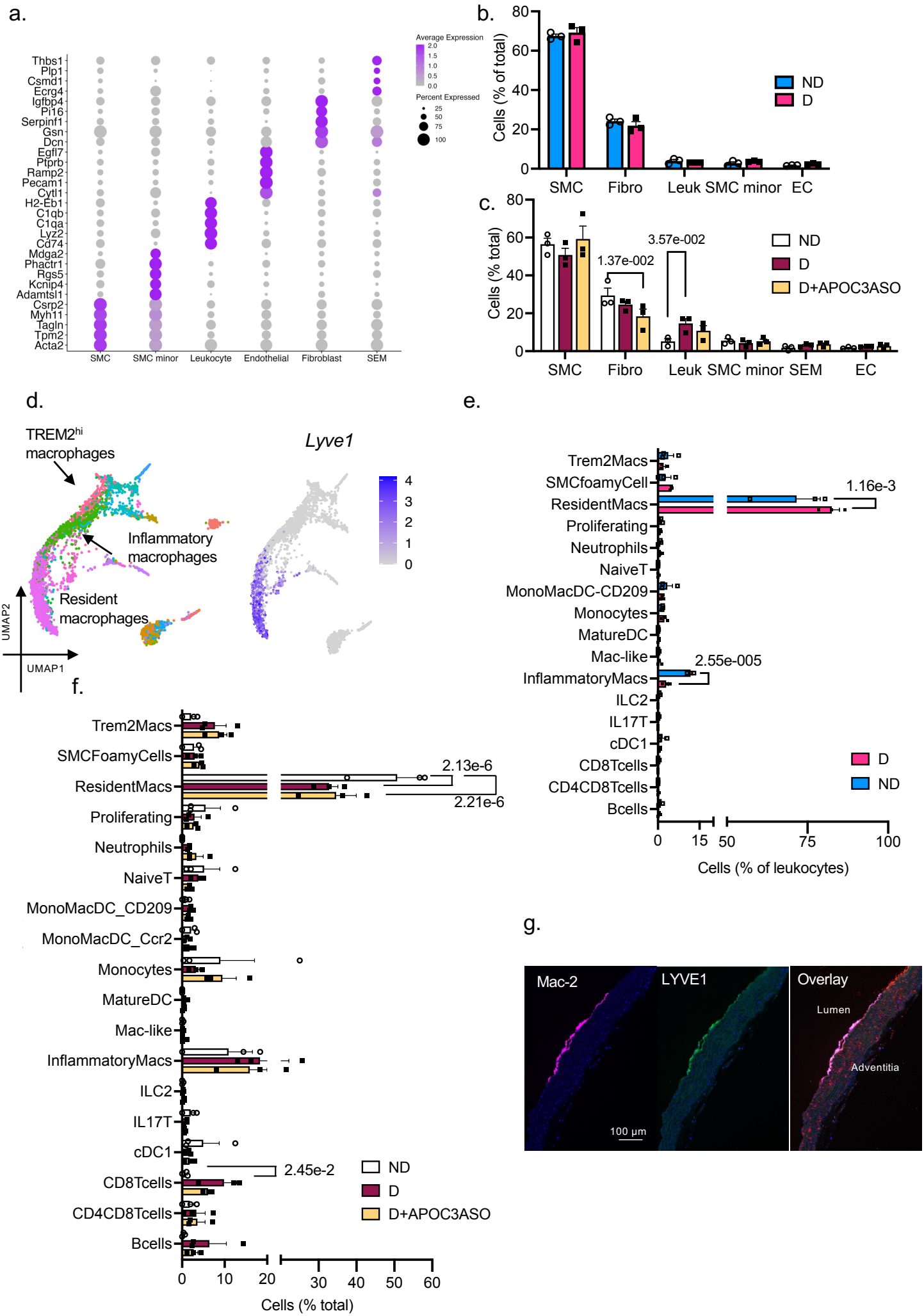
Extended Data Figure 4. Hepatic silencing of APOC3 lowers both TRL/RLP- and LDL- cholesterol and triglyceride, while ANGPTL3 silencing results in beneficial effects primarily on triglyceride parameters in diabetes. Diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After the onset of diabetes, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 12 weeks and injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO), apolipoprotein C3 (APOC3) or angiopoietin-like protein 3 (ANGPTL3) GalNAc ASO. **a.** Hepatic *Angptl3* mRNA at the end of the study. **b.** Hepatic *Apoc3* mRNA. The increased hepatic *Angptl3* mRNA and plasma ANGPTL3 in this diabetes model versus the STZ model of diabetes (Extended Data Fig. 3j) is likely due to the more severe hyperlipidemia (Extended Data Fig. 2c-f). Likewise, the reduction in hepatic *Angptl3* mRNA and plasma ANGPTL3 levels with APOC3 ASO are likely due to the lipid-lowering effects of APOC3 ASO. **c**. Plasma APOC3 levels. **d**. Plasma ANGPLT3 levels. **e**. Plasma triglycerides (TG) measured every 4 weeks. **f**. Plasma cholesterol measured every 4 weeks. **g**. Cholesterol lipoprotein profile. Please note that large chylomicrons were filtered out before running the FPLC. **h**. Triglyceride lipoprotein profile. **i**. Total APOB in the TRL density fraction (density <1.019 g/mL). **j**. Cholesterol in TLRs. **k**. Triglyceride (TG) in TRLs. **l**. Total APOB in LDL (density 1.08-1.019 g/mL). **m**. TG in the LDL density fraction. **n**. Cholesterol in the LDL density fraction. **o**. Blood glucose measured every 4 weeks. **p**. Hepatic TG content. **q**. Hepatic cholesterol content. Data are expressed as mean ± SEM, two-way ANOVA. Because the same cASO control mice were used for APOC3 ASO- and ANGPTL3 ASO-treated mice, all 6 groups are shown here, while only the cASO and APOC3 ASO groups are shown in Fig. 1. All statistical analyses in Figure 1 are based on the 6 group comparisons. See also Original Data Supplement.


cASO
APOC3 ASO
ANGPTL3 ASO
a.
TRL APOB100 (AU/mL)
8.35e-005
1.30e-005
5.18e-004
1.48e-002
7.22e-003
9.19e-005
b.
TRL APOC1 (AU/mL)
2.32e-003
1.24e-004
3.60e-002
3.80e-004
c.
TRL APOC2 (AU/mL)
1.83e-002
1.69e-003
5.30e-003
d.
TRL APOC3 (AU/mL)
8.37e-004
9.36e-006
4.76e-003
3.28e-008
3.14e-002
1.60e-003
e.
TRL APOC4 (AU/mL)
9.53e-003
1.39e-003
4.63e-003
f.
TRL APOE (AU/mL)
2.34e-003
1.62e-003
3.71e-002
g.
TRL APOC1/total APOB
5.84e-004
2.80e-002
3.85e-003
9.05e-003
h.
TRL APOC2/total APOB
9.30e-003
4.25e-002
i.
TRL APOC3/total APOB
4.56e-002
5.15e-004
5.19e-003
j.
TRL APOC4/total APOB
k.
TRL APOE/tota APOB
1.58e-005
4.40e-004
2.59e-004
1.89e-003
3.25e-002
l.
LDL APOB100 (AU/mL)
1.70e-004
1.14e-003
1.06e-004
m.
LDL APOC1 (AU/mL)
1.76e-006
2.27e-003
2.18e-002
3.58e-006
1.65e-002
n.
LDL APOC2 (AU/mL)
1.58e-005
2.83e-003
5.26e-005
4.17e-002
o.
LDL APOC3 (AU/mL)
3.87e-007
1.38e-003
4.73e-003
4.72e-008
2.23e-003
p.
LDL APOC4 (AU/mL)
1.74e-005
1.32e-003
1.28e-004
4.44e-002
q.
LDL APOE (AU/mL)
4.51e-005
6.33e-006
5.23e-003
9.53e-005
r.
LDL APOC1/total APOB
3.25e-003
9.64e-003
2.01e-002
4.27e-002
s.
LDL APOC2/total APOB
6.39e-006
1.25e-004
7.19e-004
4.29e-003
t.
LDL APOC3/total APOB
1.55e-003
5.70e-003
2.39e-003
3.86e-003
u.
LDL APOC4/total APOB
1.04e-004
6.84e-003
9.10e-003
v.
LDL APOE/total APOB
4.16e-009
2.55e-003
3.42e-004
2.88e-003
1.69e-005
ND
D

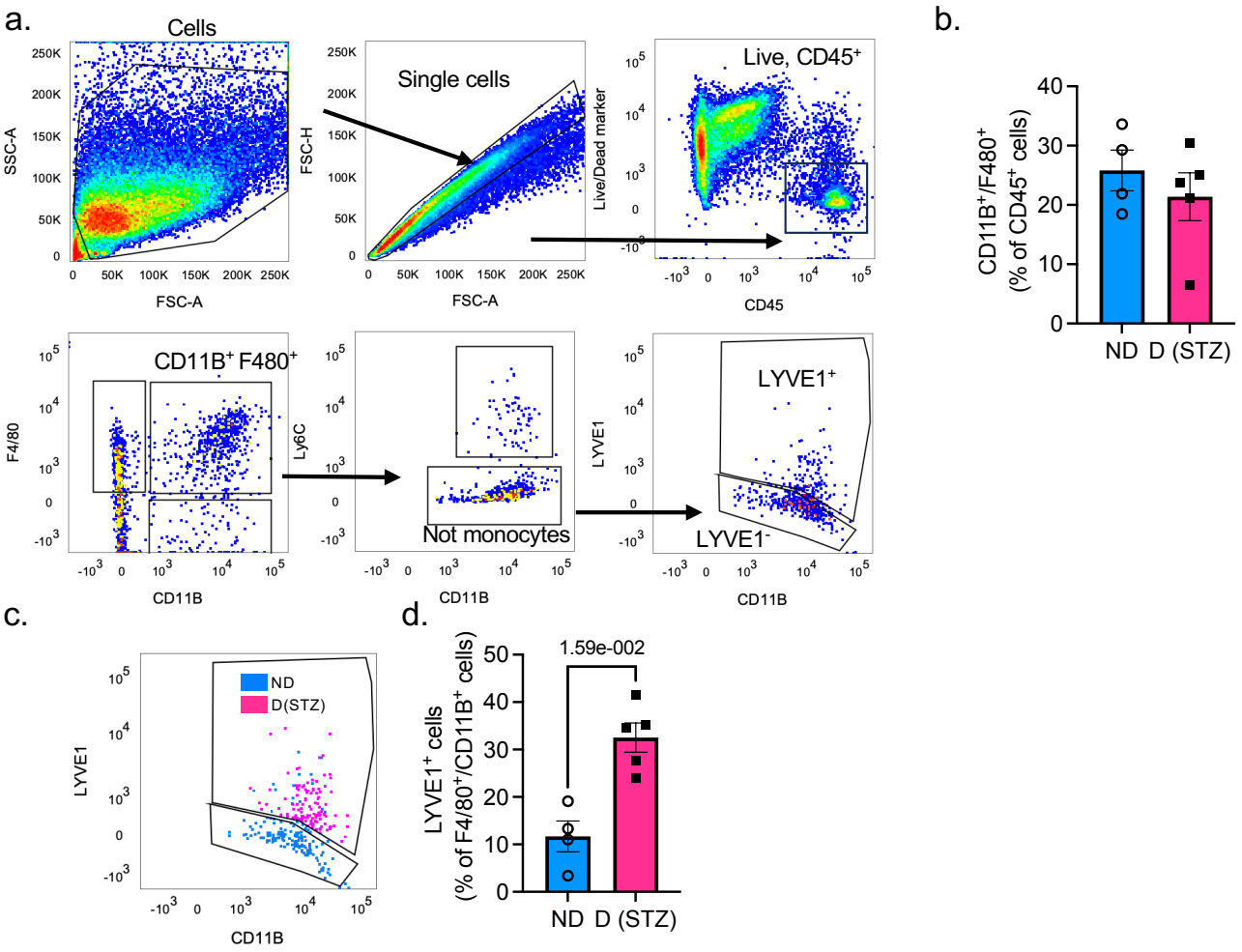
Extended Data Figure 5. Hepatic APOC3 silencing, but not ANGPTL3 silencing, normalizes TRL/RLP and LDL protein composition in diabetic mice. Diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After the onset of diabetes, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 12 weeks and injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO), apolipoprotein C3 (APOC3) or angiopoietin-like protein 3 (ANGPTL3) GalNAc ASO. **a-f.** TRL/RLP (density <1.019 g/mL with large chylomicrons removed before isolation) proteins measured by targeted mass spectrometry. Please note that the total APOB data are presented in Extended Data Figure 4i. **g-k**. TRL/RLP proteins normalized to total APOB (APOB N-terminal peptides; i.e., normalized per TRL/RLP particle). **l-q.** LDL (density 1.018-1.019 g/mL) proteins measured by targeted mass spectrometry. Please note that the total APOB data are presented in Extended Data Figure 4l. **r-v**. LDL proteins normalized to total APOB (APOB N-terminal peptides). Data are expressed as mean ± SEM, two-way ANOVA. Because the same cASO control mice were used for APOC3 ASO- and ANGPTL3 ASO-treated mice, all 6 groups are shown here, while only the cASO and APOC3 ASO groups are shown in Fig. 1. All statistical analyses in Figure 1 are based on the 6 group comparisons. See also Original Data Supplement.



Extended Data Figure 6. Hepatic silencing of APOC3 and ANGPTL3 results in distinct effects on aortic lipid accumulation in diabetes. Diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After the onset of diabetes, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 12 weeks and injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO), apolipoprotein C3 (APOC3) or angiopoietin-like protein 3 (ANGPTL3) GalNAc ASO. **a.** Sudan IV-positive aortic area in the six groups of mice. **b**. Examples and enumeration of *en face* aortic Sudan IV staining. **c**. Cross-sectional analysis of atherosclerotic lesions in the brachiocephalic artery was performed every 30 μm from the aortic origin. **d**. Aortic total cholesterol. **e**. Aortic free cholesterol. **d**. Aortic cholesteryl ester (CE). **g**. Aortic triglycerides. Data are expressed as mean ± SEM, two-way ANOVA followed by Tukey's multiple comparisons test. Because the same cASO control mice were used for APOC3 ASO- and ANGPTL3 ASO-treated mice, all 6 groups are shown here, while only the cASO and APOC3 ASO groups are shown in Fig. 1. All statistical analyses in Figure 1 are based on the 6 group comparisons. See also Original Data Supplement.

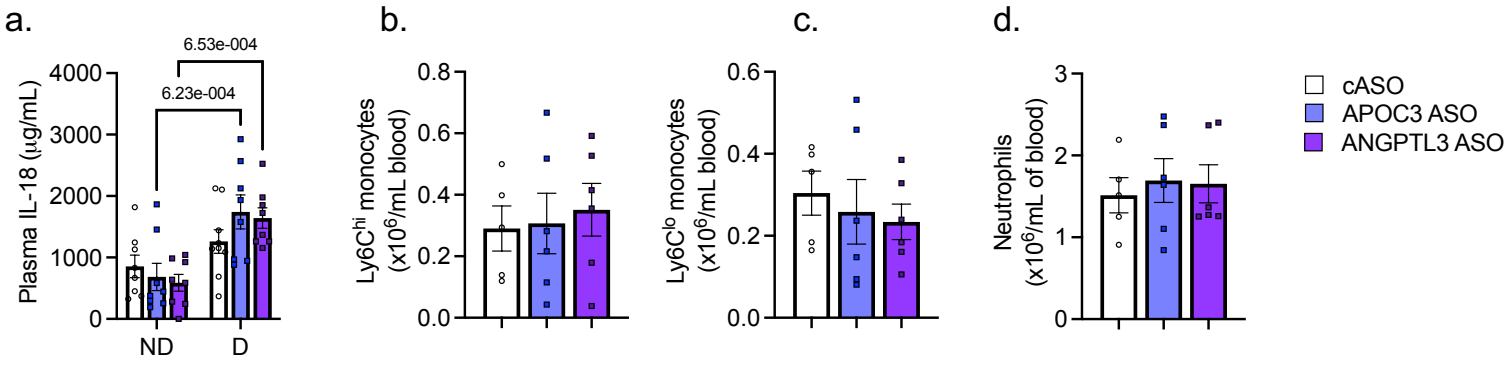

a.
Thbs1
Plp1
Csmd1
Ecrg4
Igfbp4
Pi16
Serpinf1
Gsn
Dcn
Egfl7
Ptprb
Ramp2
Pecam1
Cytl1
H2-Eb1
C1qb
C1qa
Lyz2
Cd74
Mdga2
Phactr1
Rgs5
Kcnip4
Adamtsl1
Csrp2
Myh11
Tagln
Tpm2
Acta2
SMC
SMC minor
Leukocyte
Endothelial
Fibroblast
SEM
Average Expression
Percent Expressed
b.
Cells (% of total)
ND
D
SMC
Fibro
Leuk
SMC minor
EC
c.
Cells (% total)
1.37e-002
3.57e-002
ND
D
D+APOC3ASO
SMC
Fibro
Leuk
SMC minor
SEM
EC
d.
TREM2hi macrophages
Inflammatory macrophages
Resident macrophages
Lyve1
UMAP2
UMAP1
e.
Trem2Macs
SMCfoamyCell
ResidentMacs
Proliferating
Neutrophils
NaiveT
MonoMacDC-CD209
Monocytes
MatureDC
Mac-like
InflammatoryMacs
ILC2
IL17T
cDC1
CD8Tcells
CD4CD8Tcells
Bcells
1.16e-3
2.55e-005
D
ND
Cells (% of leukocytes)
f.
Trem2Macs
SMCFoamyCells
ResidentMacs
Proliferating
Neutrophils
NaiveT
MonoMacDC_CD209
MonoMacDC_Ccr2
Monocytes
MatureDC
Mac-like
InflammatoryMacs
ILC2
IL17T
cDC1
CD8Tcells
CD4CD8Tcells
Bcells
2.13e-6
2.21e-6
2.45e-2
ND
D
D+APOC3ASO
Cells (% total)
g.
Mac-2
LYVE1
Overlay
Lumen
Adventitia
100 μm

Extended Data Figure 7. The increased levels of TRLs/RLPs in diabetic mice have no consistent effect on the relative abundance of cell populations in lesioned aortas. Diabetes was induced using low-dose streptozotocin (STZ; 50 mg/kg for five days) in female *Ldlr*$^{-/-}$ mice. Alternatively, diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After diabetes onset, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 9 (STZ) or 12 (LCMV) weeks. The autoimmune LCMV model of diabetes was injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO) or apolipoprotein C3 (APOC3) GalNAc ASO. Lesioned aortic arches from 3 biological replicates from the two models of diabetes, their littermate controls, and cASO and APOC3 ASO-treated diabetic mice (autoimmune model) were analyzed by scRNA-seq. Non-diabetic (ND) littermate controls from this model were treated with cASO. **a.** The top 5 differentially expressed genes (DEG) in each cluster (see also Supplemental Excel 1-2). **b.** Cell populations in the STZ model based on scRNA seq clustering **c**. Cell populations in the LCMV model based on scRNA seq clustering. **d**. Reclustering of the leukocyte population in the LCMV model with *Lyve1* expression highlighted on the right. **e-f**. Quantification of the relative abundance of the reclustered leukocyte populations in the STZ model (e) and LCMV model (f). **g**. Immunohistochemistry of aortic arch cross sections stained for Mac-2 and LYVE1. Data are expressed as mean ± SEM. Statistical analysis by two-way ANOVA. See also Original Data Supplement.



Extended Data Figure 8. Diabetes results in increased abundance of a LYVE1^{+} aortic macrophage population, without an increase in total macrophages in the STZ model. Diabetes was induced using low-dose streptozotocin (STZ; 50 mg/kg for five days) in female *Ldlr-/-* mice. After diabetes onset, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 9 weeks. **a.** Example of aortic flow cytometry gating. Live, CD45^{+} cells were identified, followed by CD11B and F4/80-double positive cells. From there, the Ly6C^{hi} cells (monocytes) were excluded, and then LYVE1^{hi} and LYVE1^{lo} cells were identified. **b**. Quantification of CD11B and F4/80-double positive cells, as % of CD45-positive cells (data are similar if expressed as % of single cells). **c-d**. Quantification of the proportion of macrophages that are LYVE1-positive in ND and D mice. Data are expressed as mean ± SEM, Mann-Whitney test (b, d). See also Original Data Supplement.

Extended Data Figure 9. Predicted upstream regulators in arterial cells in both models of diabetes prevented by hepatic APOC3 silencing. Diabetes was induced using low-dose streptozotocin (STZ; 50 mg/kg for five days) in female *Ldlr*$^{-/-}$ mice. Alternatively, diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After diabetes onset, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 9 weeks (STZ), or 12 weeks (LCMV) while also injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO) or apolipoprotein C3 (APOC3) GalNAc ASO. Lesioned aortic arches from 3 biological replicates from the two models of diabetes and cASO and APOC3 ASO-diabetic mice and ND cASO controls were analyzed by scRNA-seq and subsequent IPA analysis for predicted upstream regulators. **a.** Upstream regulator analysis in the resident macrophage cluster (n=3). Only upstream regulators with enrichment scores of ≥2 or ≤-2 in all comparisons and adjusted p values of $p<0.05$ are shown. **b.** Upstream regulator analysis in the endothelial cells cluster (n=3). **c.** Upstream regulator analysis in the smooth muscle cell cluster (n=3). Only upstream regulators with enrichment scores of ≥ 2 or ≤ -2 in all comparisons are shown. The size of the bubble indicates the statistical significance, while the color represents the Z-score. The full data set can be found in the Supplemental Excel 3.



Extended Data Figure 10. Lowering TRLs/RLPs in diabetic mice does not affect markers of systemic inflammation. Diabetes was induced in male *Ldlr*$^{-/-}$ *Gp*^{Tg} mice by LCMV. After diabetes onset, the mice were fed a low-fat, semi-purified diet (10% of calories from fat, no added cholesterol) for 12 weeks and injected weekly with 10 mg/kg/week control GalNAc antisense oligonucleotide (cASO), apolipoprotein C3 (APOC3) or angiopoietin-like protein 3 (ANGPTL3) GalNAc ASO. **a**. Plasma IL-18 at the end of the study. **b**. Circulating Ly6C^{hi} monocytes in diabetic mice. **c**. Circulating Ly6C^{lo} monocytes in diabetic mice. **d**. Circulating neutrophils in diabetic mice. Data are expressed as mean ± SEM. Statistical analyses were performed using two-way ANOVA followed by Tukey's multiple comparisons test (a), or Kruskal-Wallis followed by Dunn's multiple comparison tests (b-d). See also Original Data Supplement.