Supplementary Materials

1. Supplementary experimental procedures:

Hepatic Secretion of very low-density lipoprotein (VLDL)-TG. To estimate the rate of VLDL-TG secretion from the liver, mice were intraperitoneally injected with 500 mg/kg of tyloxapol (Sigma-Aldrich T0307), an inhibitor of lipoprotein lipase (LPL)[1]. Blood samples were collected from the tail vein 30 min before (time 0) and at 2, 3, and 4 h after injection. The TG concentration was determined with commercial colorimetric kits (Biolabo SAS, Maizy, France, #87656 #87319) based on the CHOD-PAP and GPO-PAP detection methods, coupling enzymatic reaction, and spectrophotometric detection of reaction end products (Dyasis, Grabels France). The TG production rate for individual mice was, therefore, calculated using the linear increment between the baseline value and 4 h and expressed as mg/dL.

1. Duerden, J.M.; Gibbons, G.F. Secretion and storage of newly synthesized hepatic triacylglycerol fatty acids in vivo in different nutritional states and diabetes. *Biochem. J.* **1988**, *255*, 929–935.

2. Supplementary Tables:

Table S1: List of qPCR primer pair sequences and GeneBank accession numbers specific to each gene.

Gene symbol	Forward primer (5'-3')	Reverse primer (5'-3')	GeneBank
Gapdh	TGCACCACCAACTGCTTAGC	GGCATGGACTGTGGTCATGAG	NM_001289726
Pgc-1α	AAAGGATGCGCTCTCGTTCA	GGAATATGGTGATCGGGAACA	NM_008904
Ucp1	CCTGCCTCTCTCGGAAACAA	TGTAGGCTGCCCAATGAACA	NM_009463
Prdm16	CAGCACGGTGAAGCCATTC	GCGTGCATCCGCTTGTG	NM_001291026
Cidea	GCCGTGTTAAGGAATCTGCTG	TGCTCTTCTGTATCGCCCAGT	NM_007702
Cd36	GCGACATGATTAATGGCACAGACG	TCCGAACACAGCGTAGATAGACC	NM_001159558.1
Acox1	CTATGGGATCAGCCAGAAAG	AGTCAAAGGCATCCACCAAAG	NM_0015729.4
Cpt1-a	CACCAACGGGCTCATCTTCT	CCTTCTATCGAATTTGCTCTGGTT	NM_013495
Acaca	AGCAACATCACATCAGTCCTGT	CAGTGTAGCTGCATGACTATCTAGG	NM_133360.3
Elovl6	TCTGATGAACAAGCGAGCCA	TGGTCATCAGAATGTACAGCATGT	NM_130450
Pparα	CCCTGTTTGTGGCTGCTATAATTT	GGGAAGAGGAAGGTGTCATCTG	NM_011144
Ehhadh	TTGGACCATACGGTTAGAGCC	GGATATCAGCACCTGCACAGA	NM_023737.3
Acaa1	ACATCTCCGTGGGCAATGTT	CTCAGAAATTGGGCGATGCG	NM_001357516.1
Atgl	TCCTTAGGAATGGCCTAC	TCCTCTTCCTGGGGGACAAC	NM_001163689.1
Hsl	GATGCCATGTTGGCCAGAGAC	ACTTCTCGAAAGCCTTCTGGAACA	XM_030242180.1
Srebp1c	CTGGCTTGGTGATGCTATGTTG	GACCATCAAGGCCCCTCAA	NM_001358315
Fas	CGGCTGCGTGGCTATGATTATG	GCAGCTTGCCTTGTTCACCTTC	NM_007988
Scd1	CGTGGGCGCGGTGAT	CAACACCATGGCGTTCCA	NM_009127.4
Elovl3	GGACCTGATGCAACCCTATGA	TCCGCGTTCTCATGTAGGTCT	NM_007703
Dgat	GGCGGTCCCCAACCAT	AGACAGGAGTGGAAAAACCAATAGA	NM_010046.3
Mttp	TCAGGAAGCTGTGTCAGAATGAAG	TTTCAAGTCCTCCCAGGATCA	NM_008642
Srebp2	CTGCAGCCTCAAGTGCAAAG	CAGTGTGCCATTGGCTGTCT	NM_033218
Hmgs1	TGCATAGTAACACAGCAACAGAGC	TGCAGGGAGTCTTGGCACTTTC	NM_001291439.1
Hmgcr	CCGGCAACAACAAGATCTGTG	ATGTACAGGATGGCGATGCA	NM_001360165
Scarb1/Srb1	CGCCGACCCTGTGTTGTC	GGATGTCTAGGAACAAGGAATGCT	NM_001205083
Ldlr	GCATCAGCTTGGACAAGGTGT	GGGAACAGCCACCATTGTTG	NM_010700
Vldlr	TCCTGATTGCGAAGACGGTTCTG	ATGCGGCATGTTCTCATATGGC	NM_001347441.1
Abca1	ATCGTGTCTCGCCTGTTCTCA	GTCCTTAATGCTGGTATCTCTTTGG	NM_013454
Cyp7A1	CAGGGAGATGCTCTGTGTTCA	AGGCATACATCCCTTCCGTGA	NM_007824
Cyp27A1	GCCTCACCTATGGGATCTTCA	TCAAAGCCTGACGCAGATG	NM_024264
Abcg5	GGATCCAACACCTCTATGCTAAA	GGCAGGTTTTCTCGATGAACTG	NM_031884
Abcg8	ATCCATTGGCCACCCTTGT	GCGTCTGTCGATGCTGGTC	NM_026180

3. Supplementary figures:

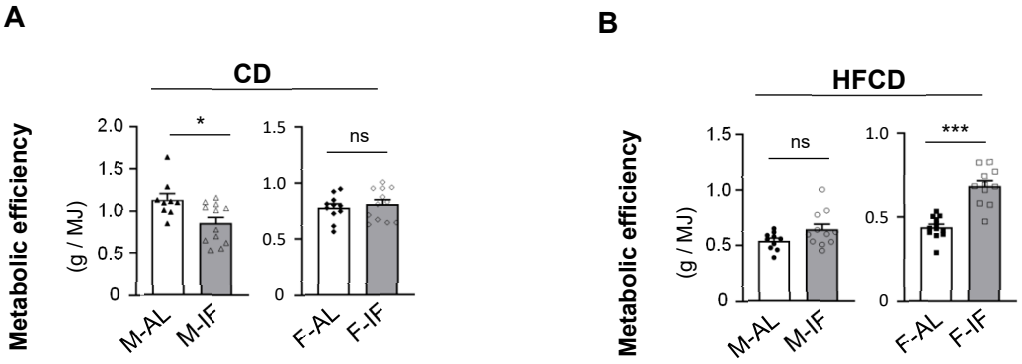

Figure S1. Effect of intermittent fasting in *Apoe*$^{-/-}$ mice on metabolic efficiency. (A–B) Metabolic efficiency was calculated as g of body weight gained per MJ of food consumed during the 16 weeks of intervention for *ad libitum* (AL) or intermittent fasting (IF) CD-fed mice (A) and HFCD-fed mice (B). Data are presented as means ± SEM (n = 12–14 per group); ns; not significant, *p < 0.05, **p < 0.01, ***p < 0.001.

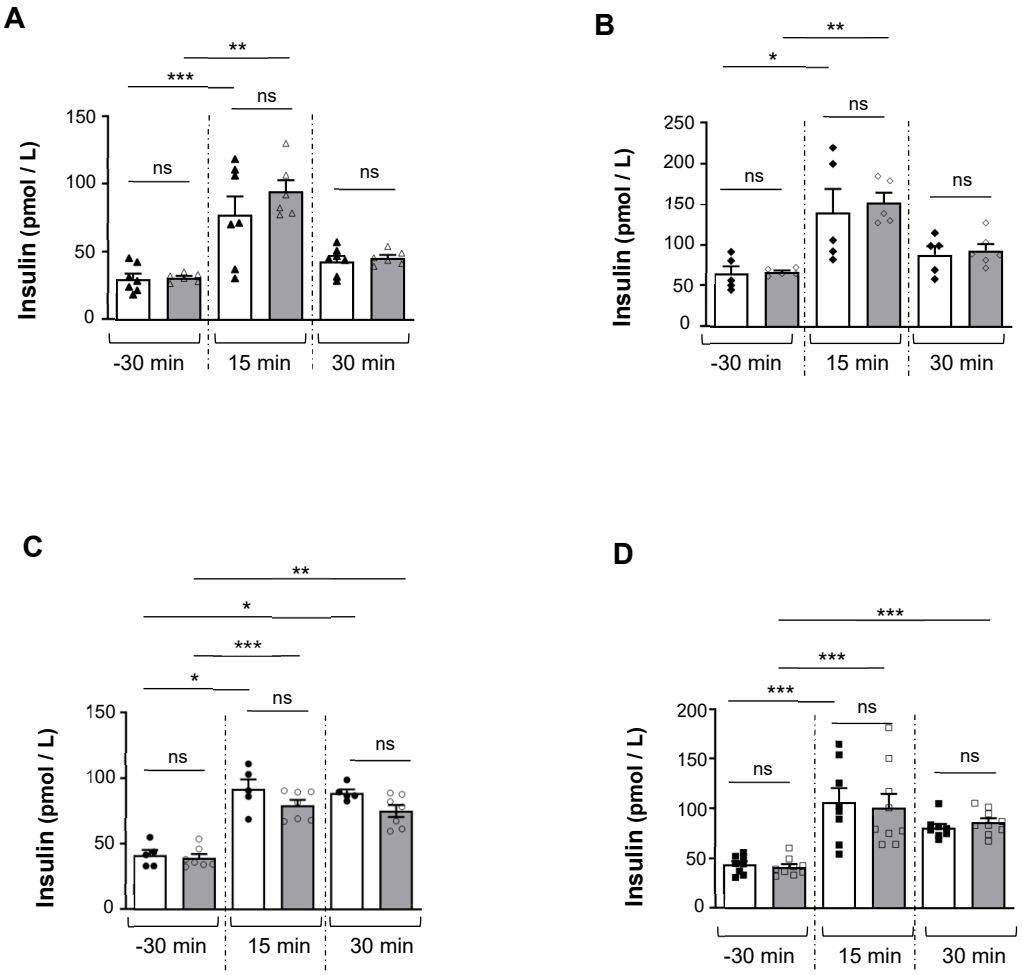

Figure S2. Effect of intermittent fasting in *Apoe*$^{-/-}$ mice on the plasma insulin level during glucose tolerance test. (A–D) Plasma insulin concentration at the indicated times after intraperitoneal bolus injection of glucose to fasted *ad libitum* (AL, white bars) or intermittent fasting (IF, grey bars) CD-fed males (A), CD-fed females (B), HFCD-fed males (C), and HFCD-fed females (D). Data are presented as means ± SEM (n = 5–9 per group); ns; not significant, *p < 0.05, **p < 0.01, ***p < 0.001.

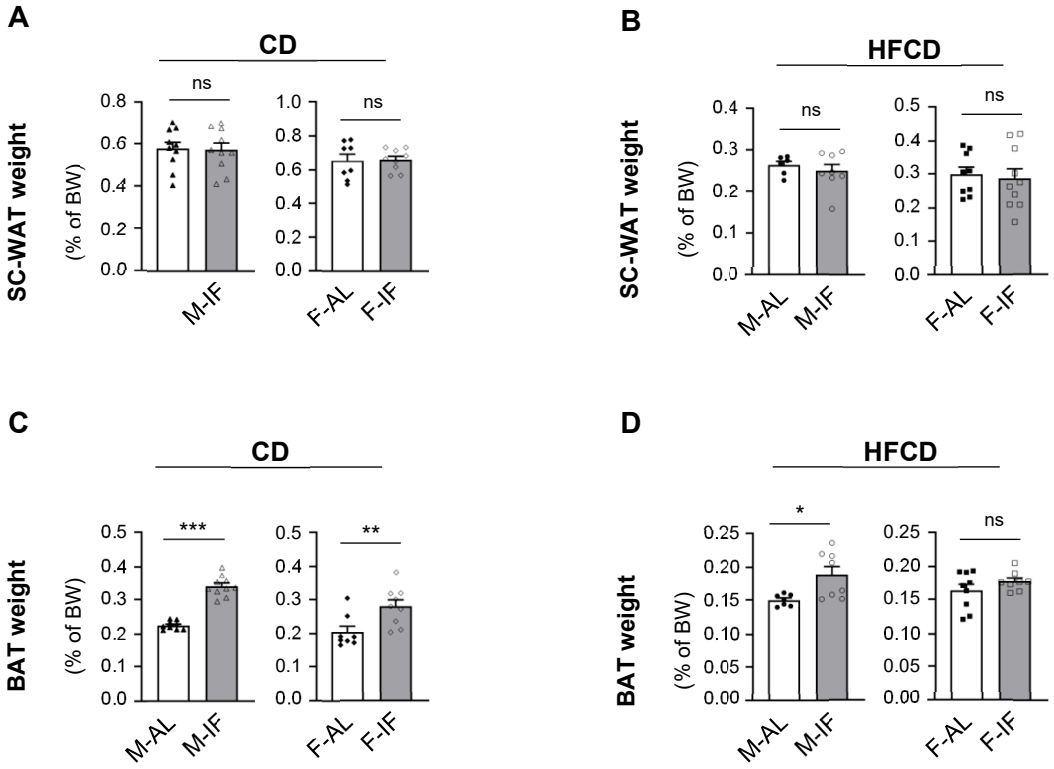

Figure S3. Effect of *intermittent* fasting in *Apoe*$^{-/-}$ mice on white and brown adipose tissue weight. (A,B) Subcutaneous white adipose tissue (SC-WAT) weights relative to body weight of *ad libitum* (AL) or intermittent fasting (IF) CD-fed mice (A) and HFCD-fed mice (B). (C,D) Brown adipose tissue (BAT), weights relative to body weight of *ad libitum* (AL) or intermittent fasting (IF) CD-fed mice (C) and HFCD-fed mice (D). Data are presented as means ± SEM (n = 6–10 per group); ns; not significant, *p < 0.05, **p < 0.01, ***p < 0.001.

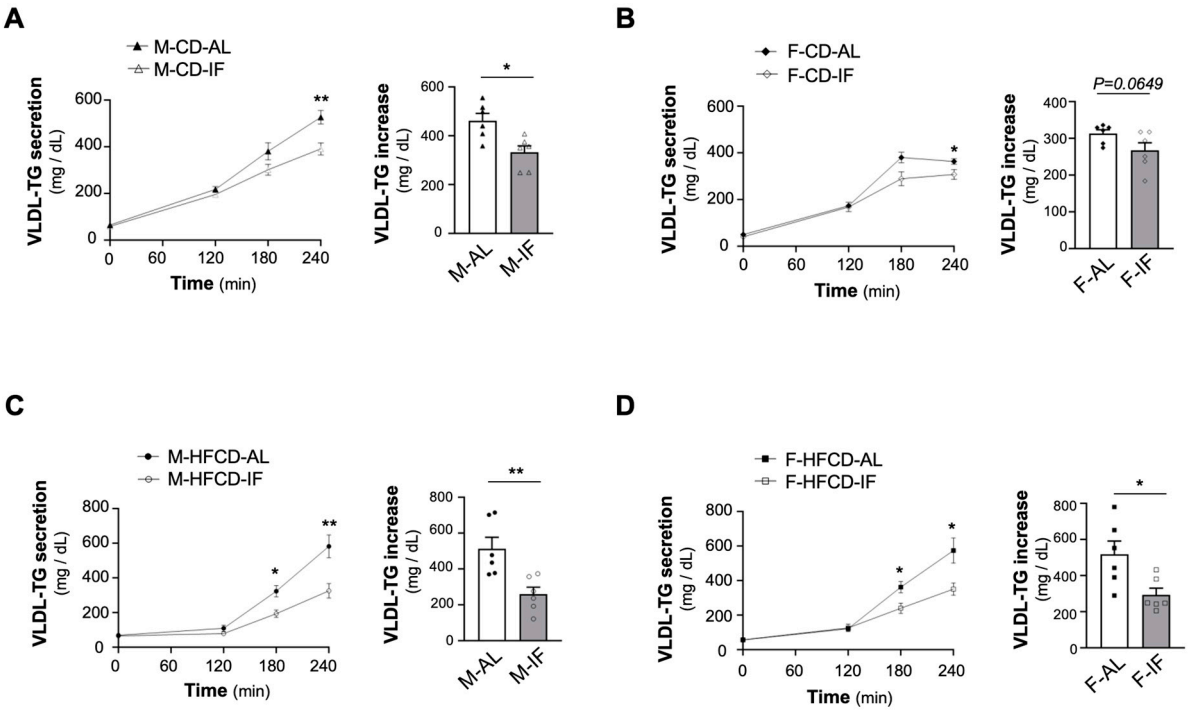

Figure S4. Effect of intermittent fasting in *Apoe*$^{-/-}$ mice on hepatic very low-density-lipoprotein (VLDL)-TG secretion. (A–D) Hepatic VLDL-TG secretion assessed at the indicated times following lipoprotein lipase inhibition by injecting 500 mg/kg of tyloxapol after a 4 h fast of *ad libitum* (AL) or intermittent fasting (IF) mice. Left panel: change in plasma VLDL-TG concentration for the indicated times, Right panel: rate of VLDL-TG secretion at 4 h. CD-fed males (A), CD-fed females (B), HFCD-fed males (C), HFCD-fed females (D). Data are means ± SEM (n = 6 per group).; ns; not significant, *p < 0.05, **p < 0.01, ***p < 0.001.