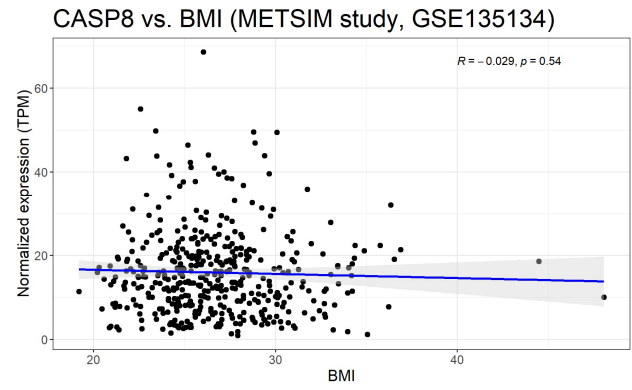
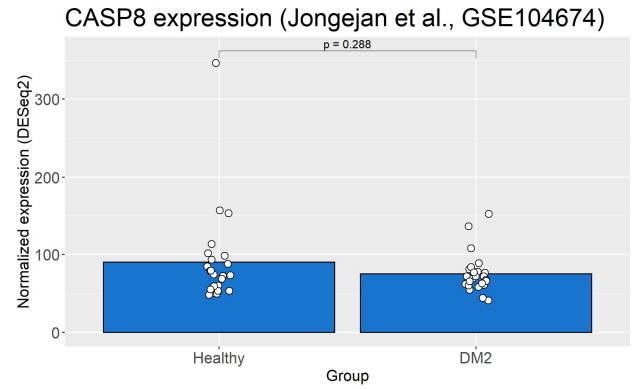
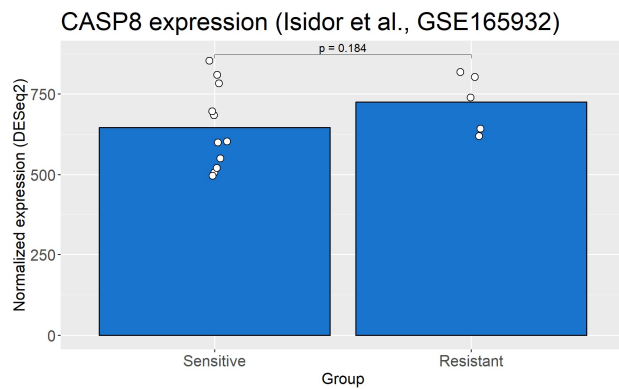
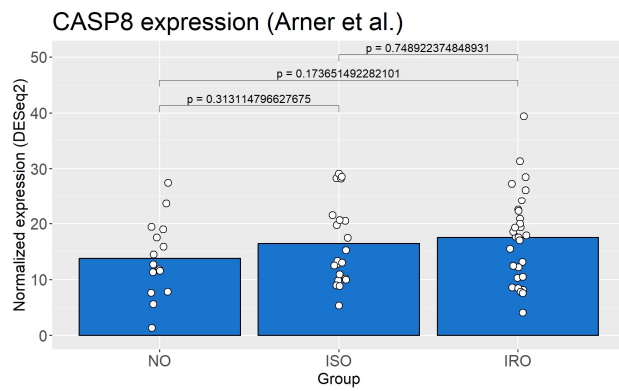
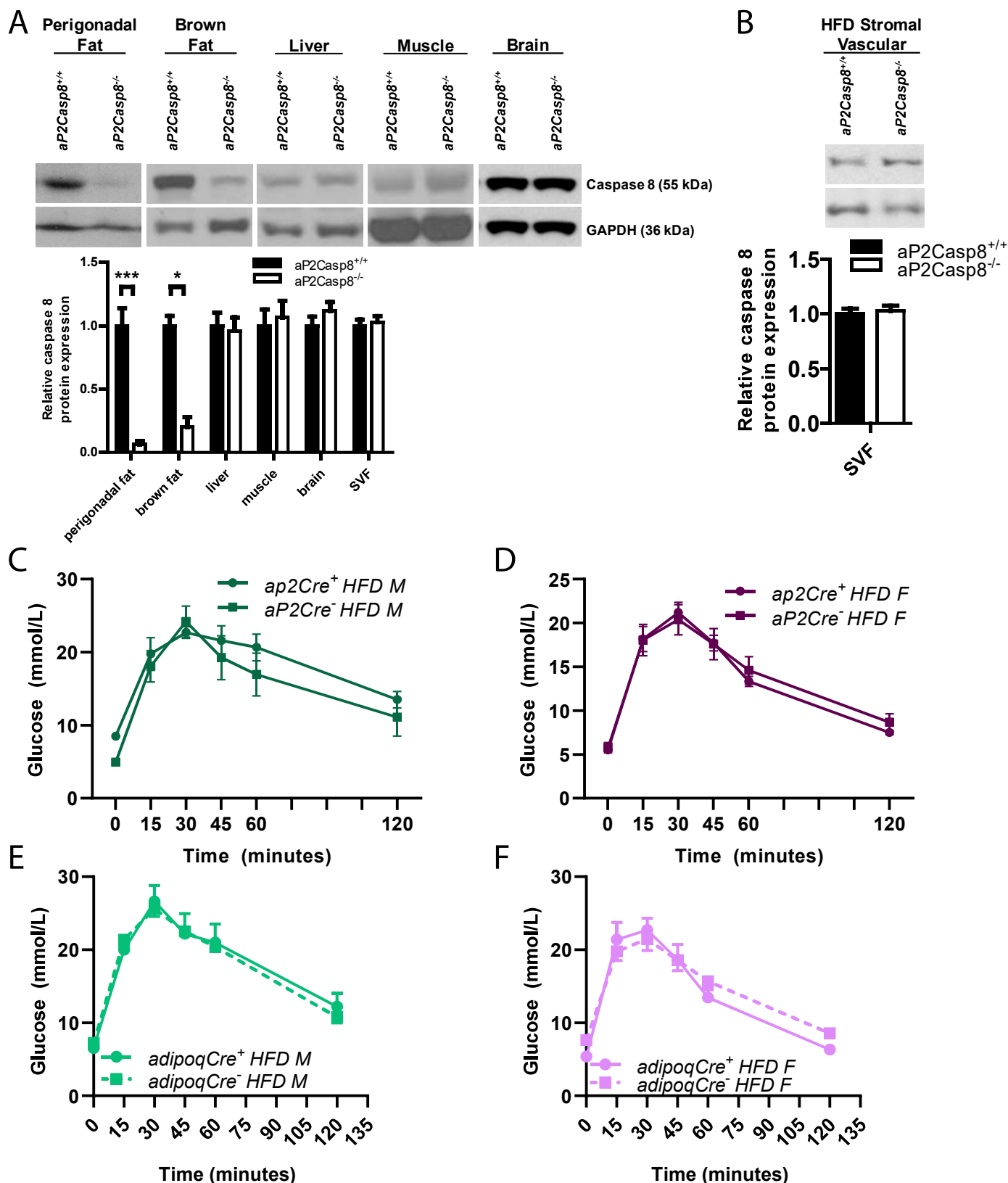


Supplementary Figure 1. Caspase 8 increases in adipose tissue with obesity and type 2 diabetes. (A) Western blots of caspase 8 protein levels in perigonadal adipose tissue from mice fed chow diet (NCD, n=4) or high fat diet (HFD, n=5). (B) Western blots of caspase 8 protein levels in omental adipocytes from humans without (n=4) or with type 2 diabetes (n=5).

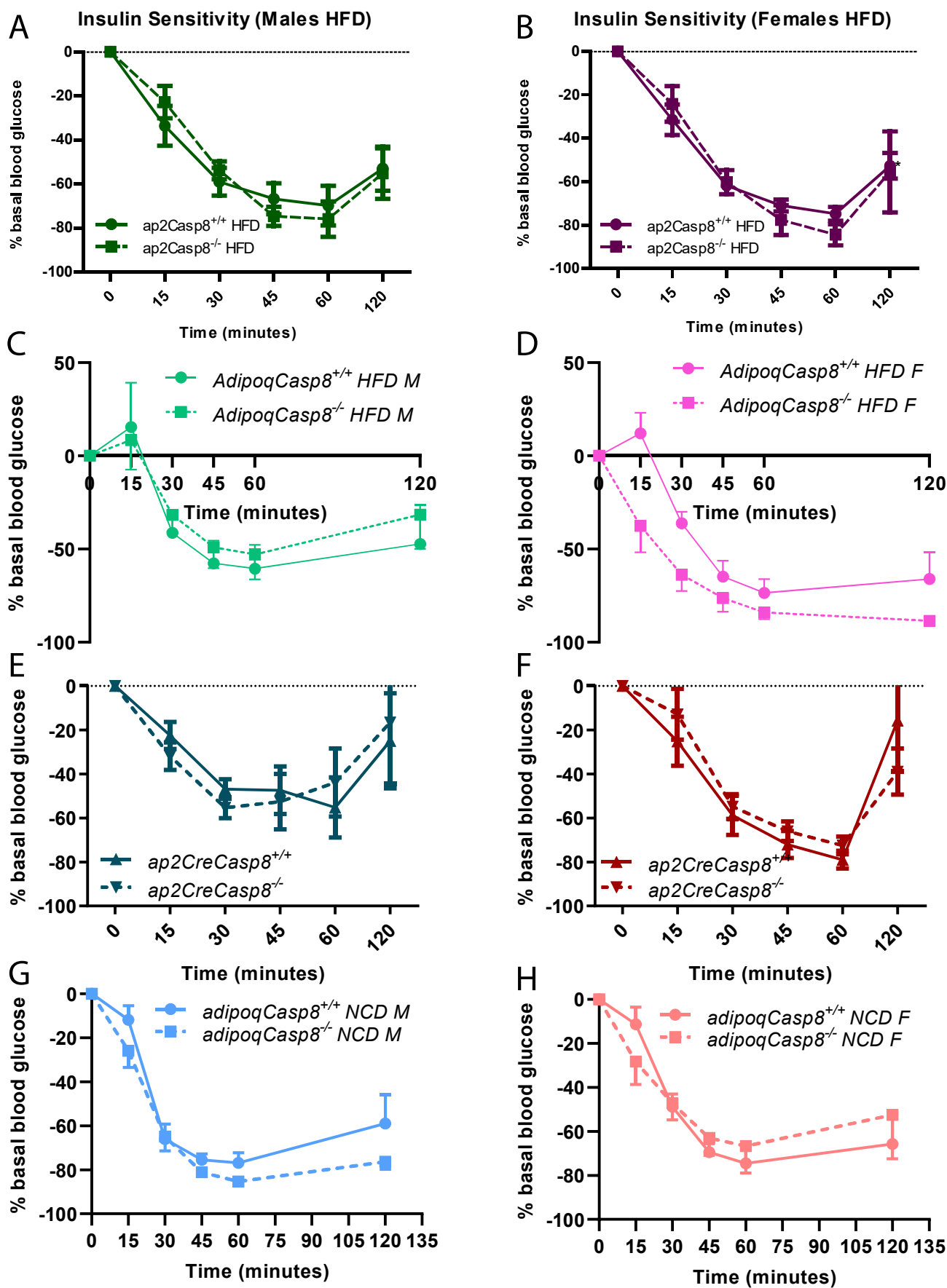


Supplementary Figure 2. Caspase 8 protein not mRNA increases in adipose tissue with obesity and type 2 diabetes. Analysis of caspase 8 mRNA expression in adipocytes from people with or without obesity or insulin resistance. Not obese (NO), insulin sensitive with obesity (ISO), insulin resistant with obesity (IRO), type 2 diabetes (DM2), female (F). p values shown using Student's t-test for two groups or Dunnett's test for three groups.

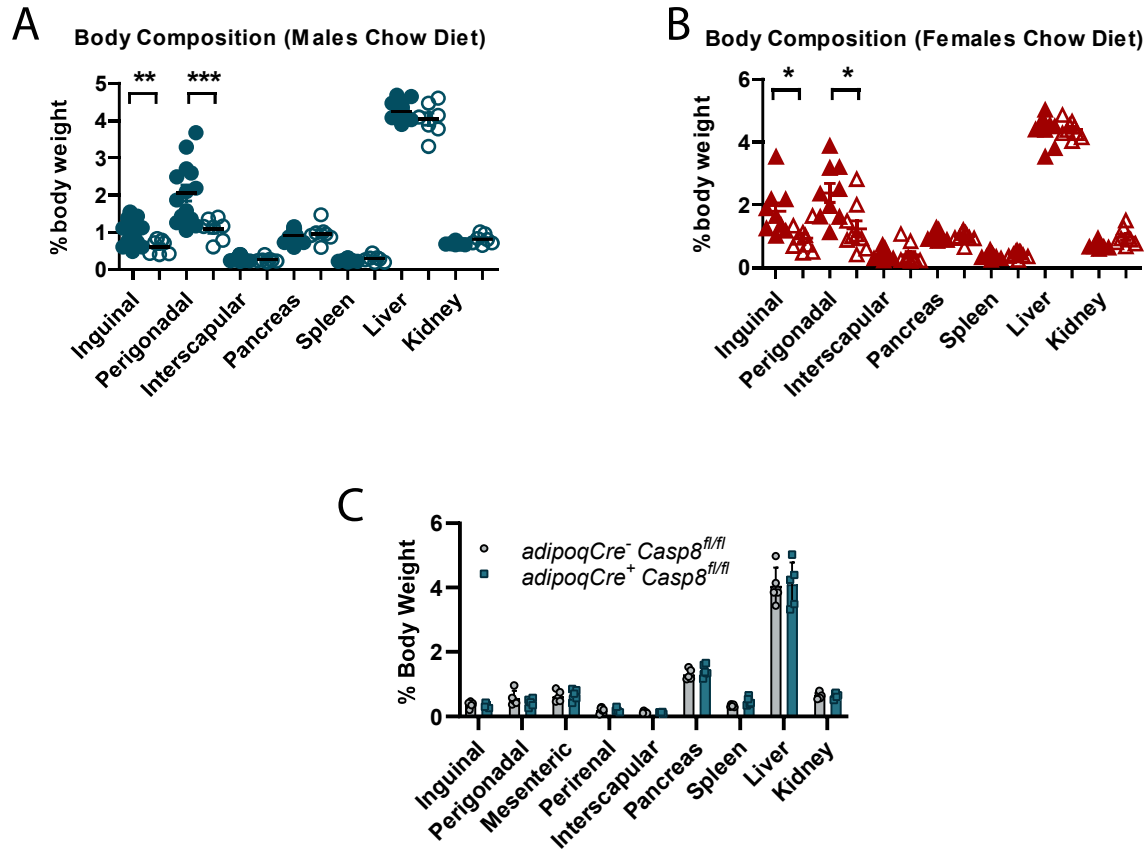


Supplementary Figure 3. Caspase 8 is deleted in *aP2Casp8*^{-/-} mouse adipose tissue. (A)

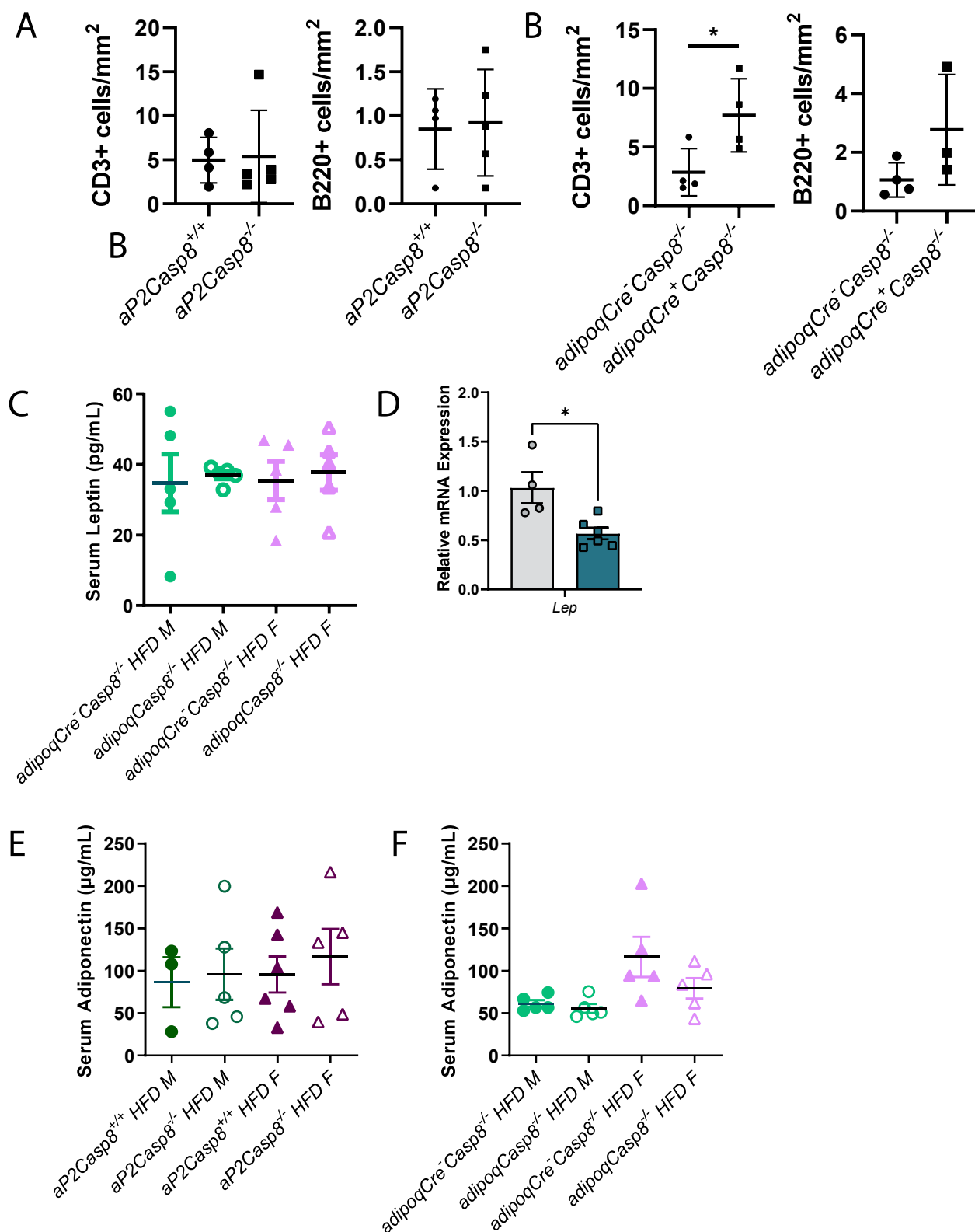
Representative Western blot and quantification of caspase 8 protein expression in white perigonadal fat, brown interscapular fat, liver, muscle and brain from *aP2Casp8*^{-/-} compared to *aP2Casp8*^{+/+} mice (n=3-6). **(B)** Representative Western blot and quantification of caspase 8 protein expression in perigonadal fat stromal vascular fraction (containing macrophages) from HFD-fed mice (n=3). **(C-F)** Intraperitoneal (IP) glucose (1 g/kg) tolerance test in male (n=6,6 for *aP2Cre*, n=6,5 for *adipoqCre*) **(C,E)** and female **(D,F)** *aP2Cre*⁺ and *aP2Cre*⁻ or *adipoqCre*⁺ and *adipoqCre*⁻ (n=6,5 for males, n=6,6 for females) mice fed HFD. Data are mean ± SEM.



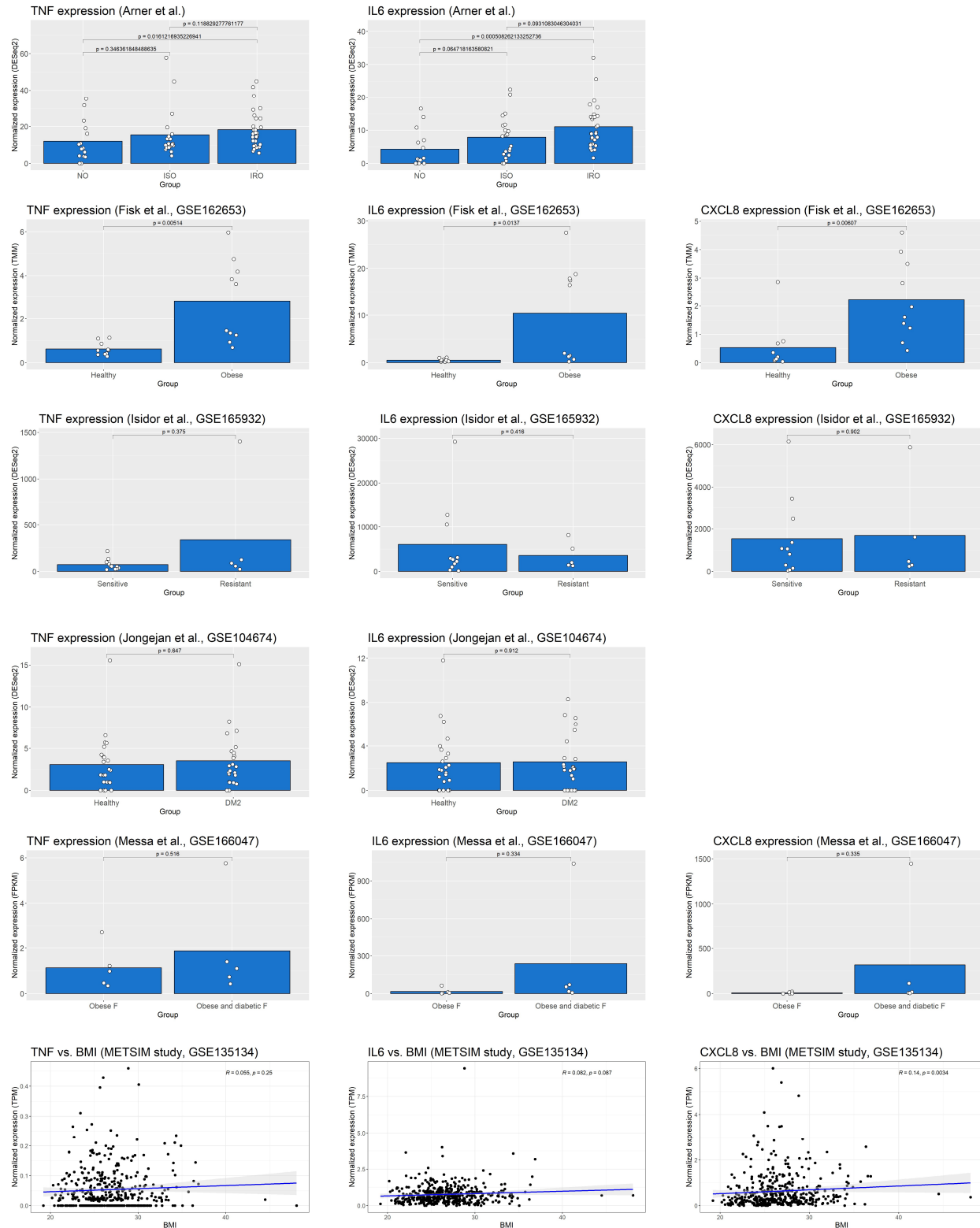
Supplementary Figure 4. Disruption of adipocyte caspase 8 improves glucose tolerance. (A-D) Insulin (1.0 U/kg) tolerance test in male (A,C) and female (B,D) *aP2Casp8*^{-/-} and *adipoqCre*⁺*Casp8*^{-/-} mice fed HFD (n=6-7). (E-H) Insulin (1.0 U/kg) tolerance test in male (E,G) and female (F,H) *aP2Casp8*^{-/-} and *adipoqCre*⁺*Casp8*^{-/-} mice fed chow diet (n=5-8).



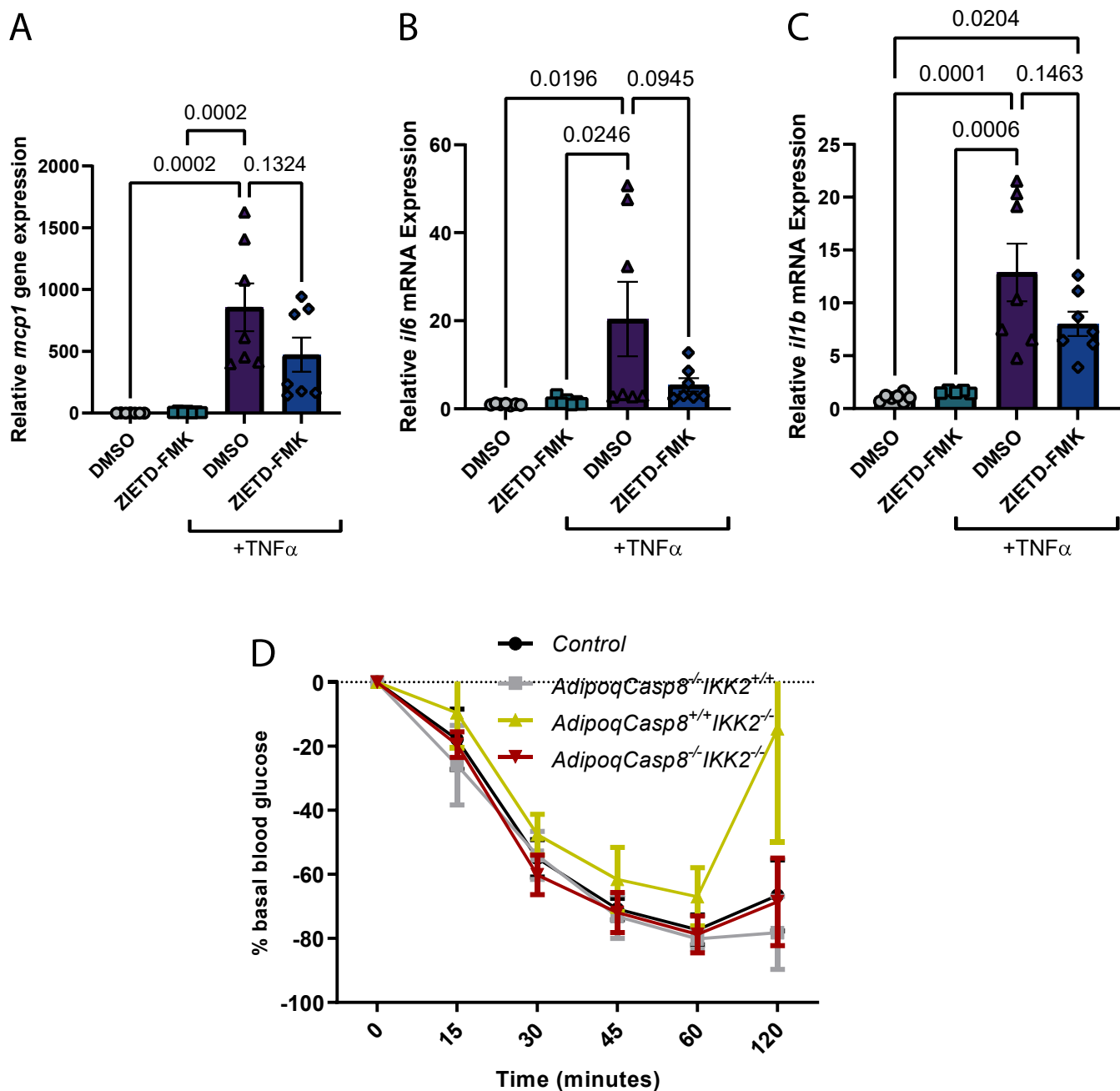
Supplementary Figure 5. Adipocyte-specific caspase 8 knockdown protects mice from weight gain on HFD. (A-C) Body composition by necropsy of male (A,C) and female (B) *aP2Casp8^{-/-}* (A,B) and *adipoqCre⁺Casp8^{-/-}* (C) mice fed chow diet (n=7-14 for *aP2Casp8^{-/-}* and n=5 for *adipoqCre⁺Casp8^{-/-}* mice). Data are mean \pm SEM. * $p \leq 0.05$, ** $p \leq 0.01$, * $p \leq 0.001$ using Student's t-test.**



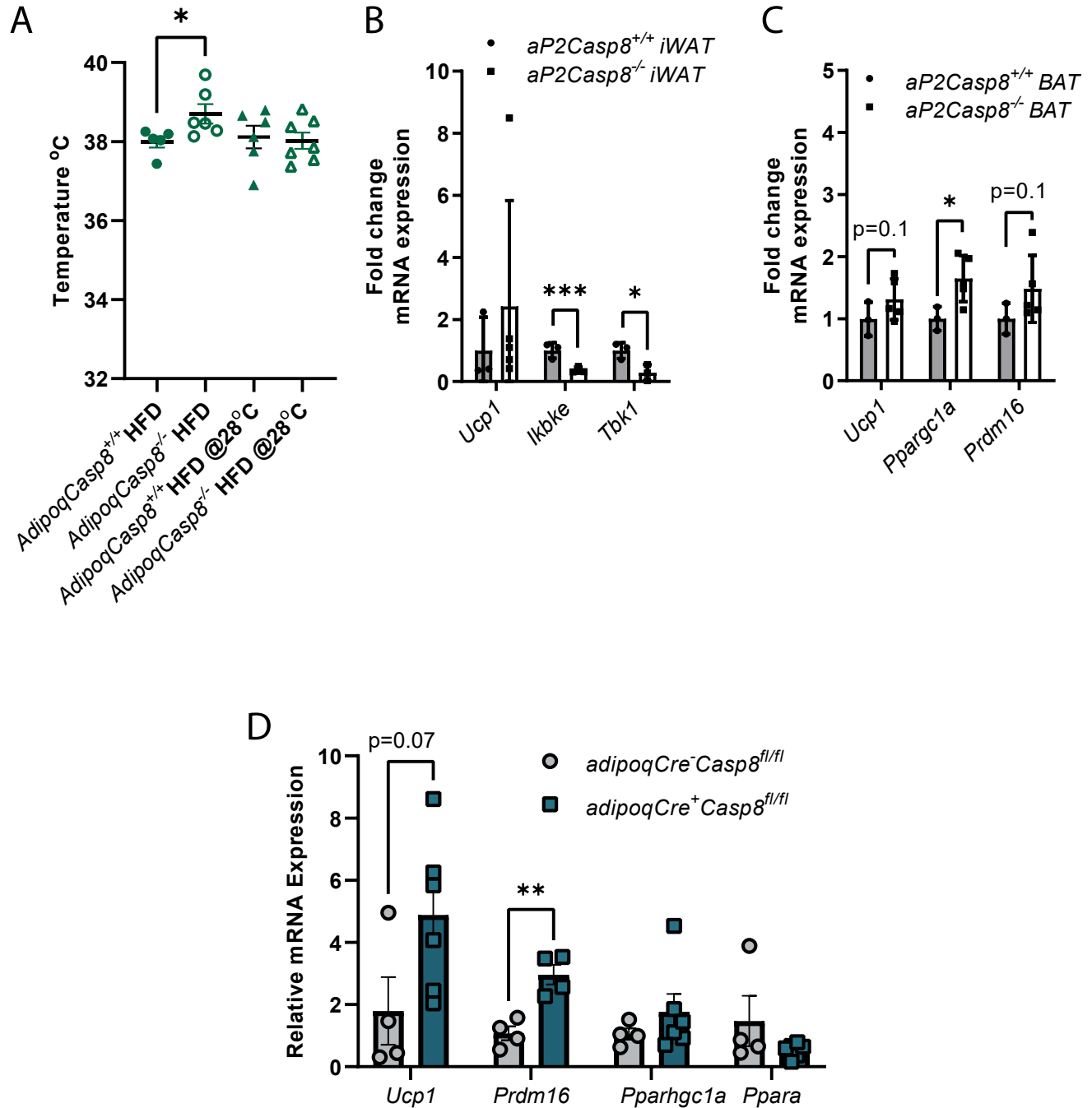
Supplementary Figure 6. Role of adipocyte caspase 8 in metabolic inflammation. (A,B) CD3 and B220 positive cells in perigonadal fat sections from HFD-fed mice stained by immunohistochemistry (n=4-6). (C) Serum leptin levels in male and female *adipoqCre⁺Casp8^{-/-}* HFD-fed mice (n=3-6). (D) Expression of leptin in perigonadal adipose tissue from *adipoqCre⁺Casp8^{-/-}* compared to control HFD-fed mice (n=4-6). (E,F) Adiponectin serum levels in male and female *aP2Casp8^{-/-}* (E) or *adipoqCre⁺Casp8^{-/-}* (F) HFD-fed mice (n=3-6). Data are mean ± SEM. * $p \leq 0.05$ using Student's t-test.



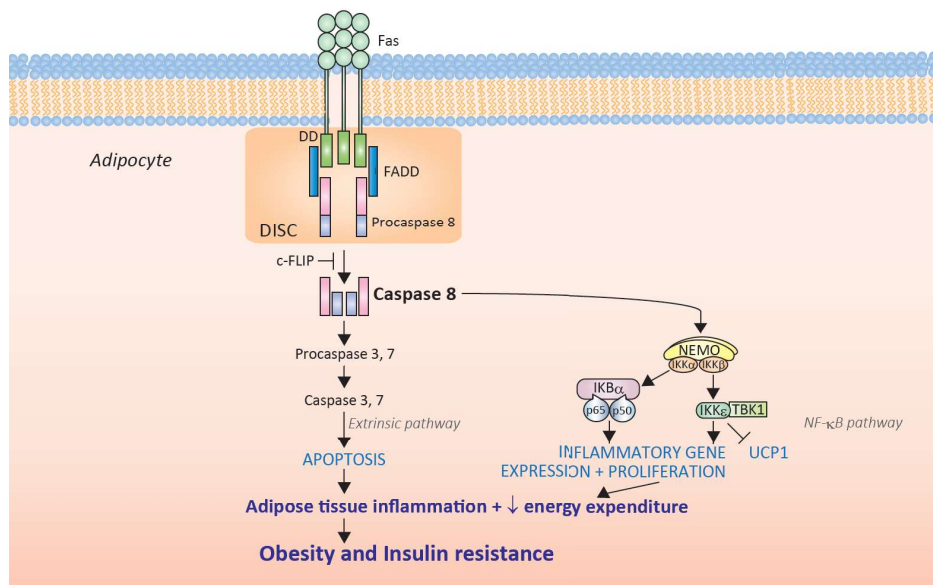
Supplementary Figure 7. Adipocyte NF- κ B target gene expression with obesity and type 2 diabetes. Analysis of NF- κ B target gene mRNA expression in adipocytes from people with or without obesity or insulin resistance. Not obese (NO), insulin sensitive with obesity (ISO), insulin resistant with obesity (IRO), type 2 diabetes (DM2), female (F). p values shown using Student's t-test for two groups or Dunnett's test for three groups.



Supplementary Figure 8. Caspase 8 regulates NF- κ B signaling in adipocytes to promote glucose intolerance. (A-C) Expression of *mcp1* (A), *il6* (B) and *il1b* (C) genes in 3T3-L1 adipocytes stimulated with $TNF\alpha$ and treated with or without caspase 8 inhibitor ZIETD-FMK (n=7 replicates, experiment repeated 3 times). (D) Insulin (1.0 U/kg) tolerance test in *adipoqCasp8^{-/-} adipoqIKK2^{-/-}* and control mice fed HFD (n=4-8). Data are mean \pm SEM. p calculated using Student's t-test.



Supplementary Figure 9. Knockdown of adipocyte caspase 8 is associated with increased energy expenditure. (A) Core body temperature in *adipoqCre⁺Casp8^{-/-}* and control mice on HFD housed at 21°C and 28°C (n=5-6). (B-D) Expression of genes involved in thermogenesis in inguinal fat (iWAT) (B), interscapular brown fat (BAT) (C) from *aP2Casp8^{-/-}* mice and perigonadal fat from *adipoqCre⁺Casp8^{-/-}* mice (D) fed HFD (n=3-6). Data are mean ± SEM. * p ≤ 0.05, ** p ≤ 0.01. *** p ≤ 0.001 using Student's t-test.



Supplementary Figure 10. Proposed working model.