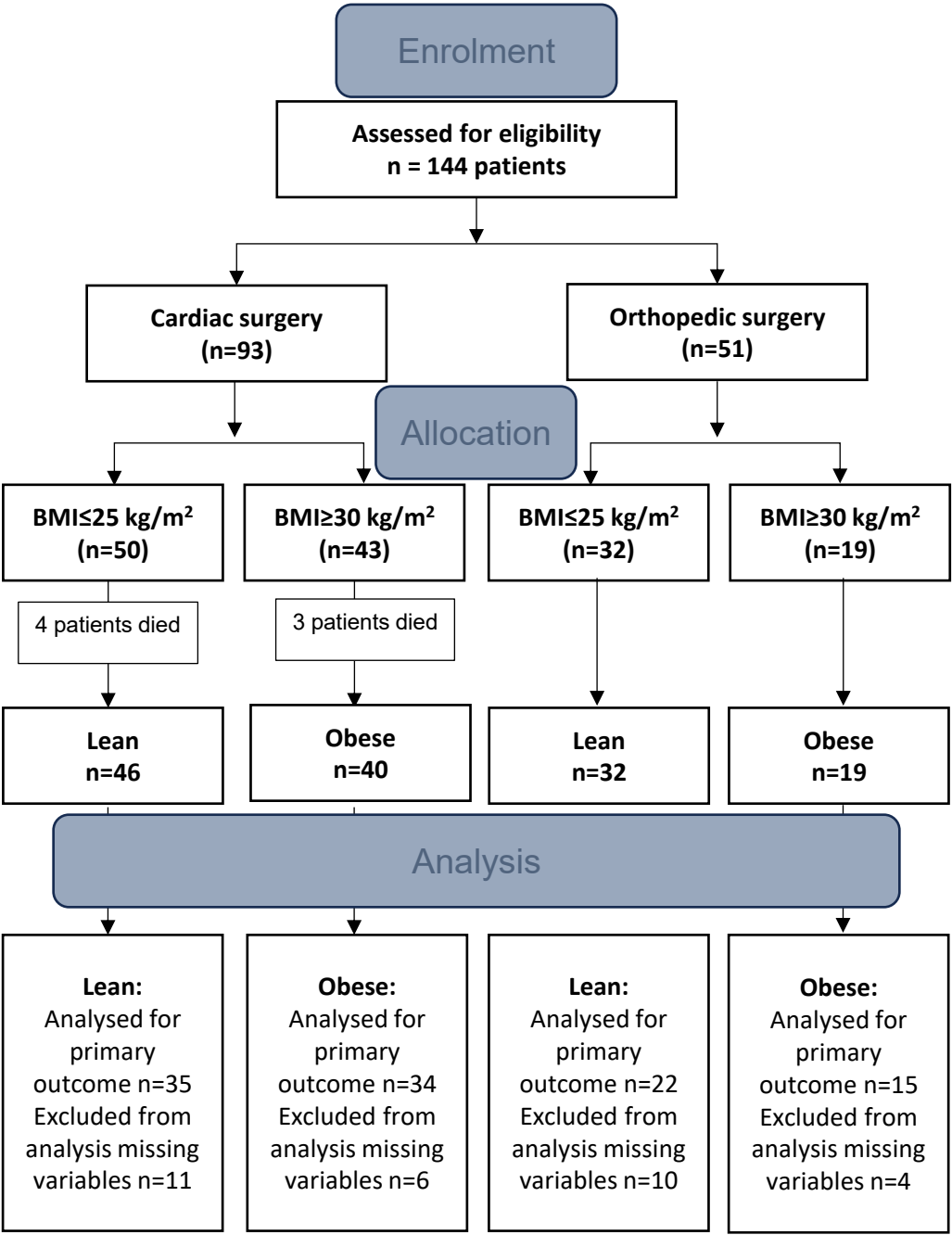
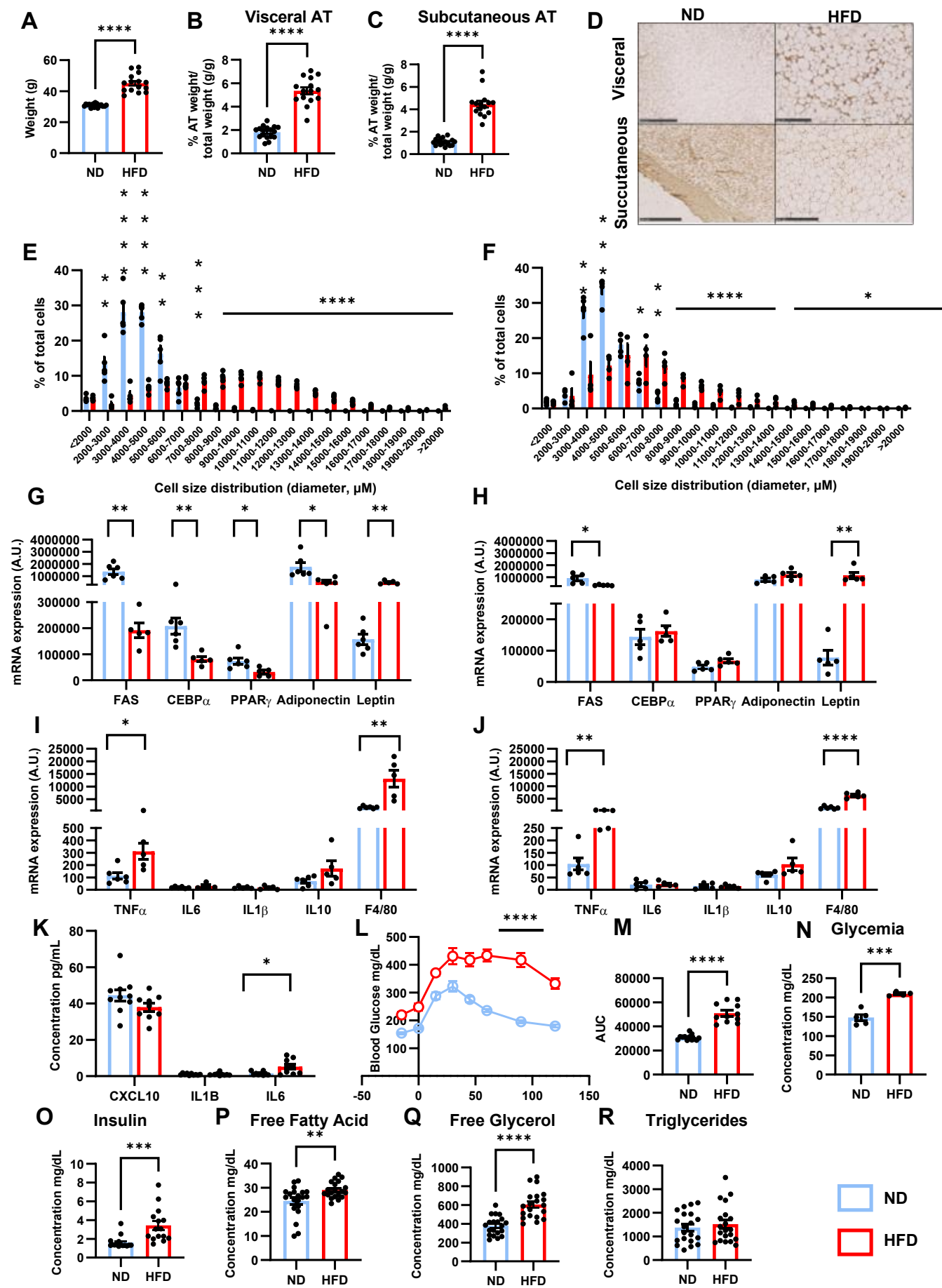


Supplemental Figure S1



Supplemental 1. CONSORT Diagram ODCOTA cohort. 106 patients were included in cardiac and orthopaedic surgeries and divided into lean and obese groups based on BMI (see Table 1).

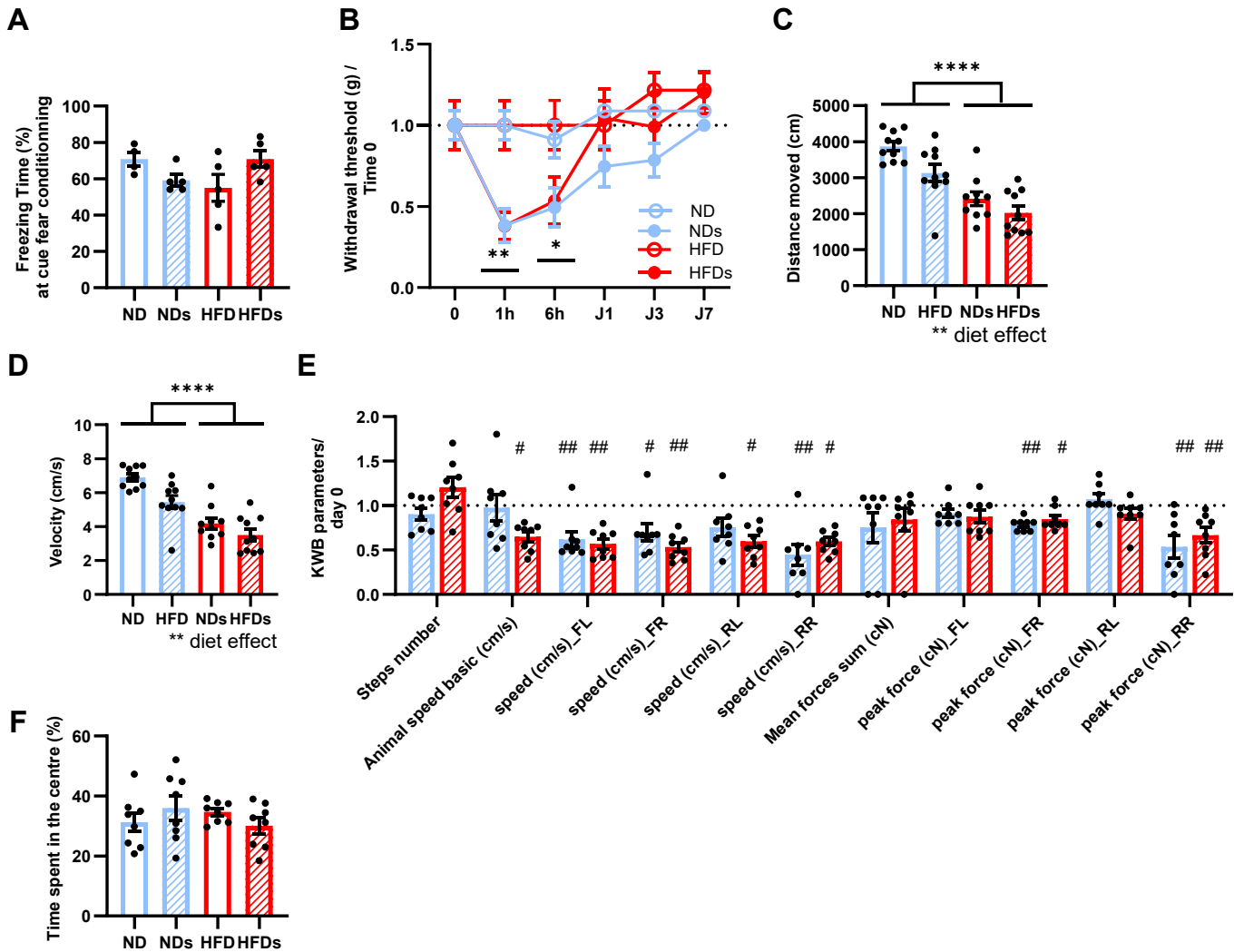
Supplemental Figure S2



Supplemental 2. Obesity phenotypic and molecular characterization.

Normal diet- and high fat diet-fed animals model validation. (A) whole body and (B) visceral or (C) subcutaneous adipose tissue weights ($n = 15-17$). (D) Representative photomicrographic images of visceral and subcutaneous adipose tissues and quantification of adipocyte size distribution measured in (E) visceral and (F) subcutaneous adipose tissues ($n = 5$, Scale bar length 500 μ m). mRNA adipogenesis genes expression measured in (G) visceral and (H) subcutaneous adipose tissues ($n = 5-6$). mRNA inflammatory genes measured in (I) visceral and (J) subcutaneous adipose tissue ($n = 5-6$). (K) Plasma cytokines levels CXCL-10, IL-1 β , IL-6 ($n = 5$). (L) Oral glucose tolerance test and (M) area under the curve ($n = 12$). (N) Plasma glucose concentration level ($n = 5$), (O) plasma insulin ($n = 15$), (P) plasma free fatty acids level, (Q) plasma free glycerol level and (R) plasma triglycerides level ($n = 20$). ND (Normal Diet) blue border, HFD (High Fat Diet) red border. Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests (A-R).

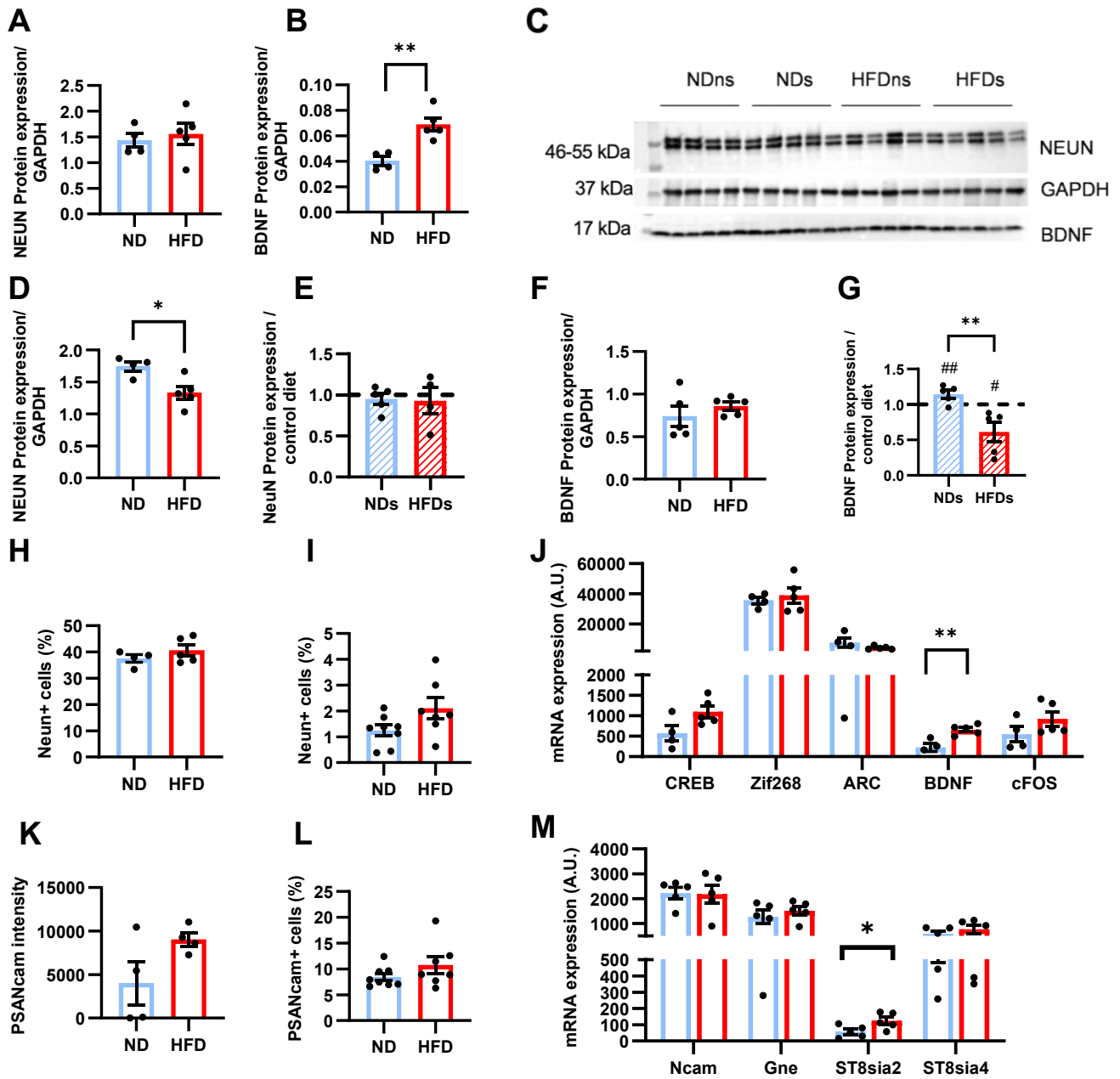
Supplemental Figure S3



Supplemental 3. Obesity promotes surgery-induced specific cognitive dysfunction in a HFD-fed mouse model of POCD.

Behavioural measure of (A) Cue fear conditioning ($n = 5$) (B) pain by the mechanical nociceptive Von Frey test ($n = 7-8$). Locomotion by (C) distanced moved, (D) velocity ($n = 10$) and (E) Kinetic Weight Bearing parameters measure ($n = 8$), and (F) anxiety with the percentage of time spent in the centre of the object location arena ($n = 8$). ND (Normal Diet no surgery) blue border, NDs (Normal Diet with surgery) blue border and pattern, HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern. Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests comparing NDs and HFDs, # $P < 0.05$, ## $P < 0.01$ analysed using Student's t -tests comparing ND to NDs or HFD to HFDs, (B), 2-way ANOVA (A, C-D, F), 1-way ANOVA (E).

Supplemental Figure S4



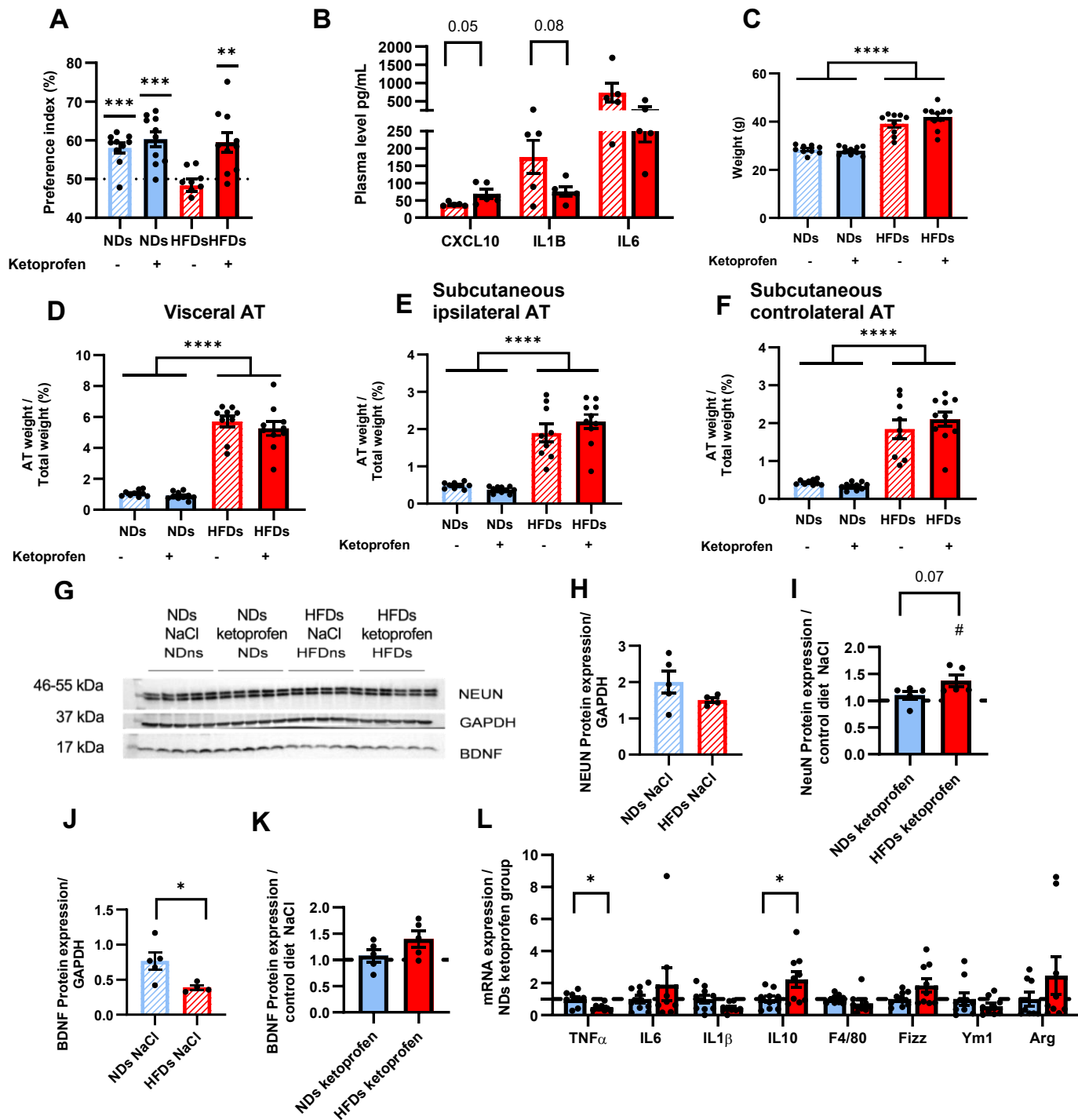
Supplemental 4. Obesity is associated with specific fracture-induced hippocampal plasticity alteration.

Hippocampal measure of central markers in control diet groups. Representative western blot protein level of NeuN and BDNF and associated quantification (A-C) 12h and (D-G) 24h post-surgery ($n = 5$). (H) Quantification of NeuN images ($n = 5$). (I) Flow cytometry measure of NeuN-positive cells ($n = 5$). mRNA level of (J) long term potentiation. (K) Quantification of PSA-Ncam images ($n=5$) and (L) flow cytometry of PSA-Ncam positive cells ($n=5$) and (M) remodelling gene ($n = 5$).

ND (Normal Diet no surgery) blue border, NDs (Normal Diet with surgery) blue border and pattern, HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern.

Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests (A-M).

Supplemental Figure S5

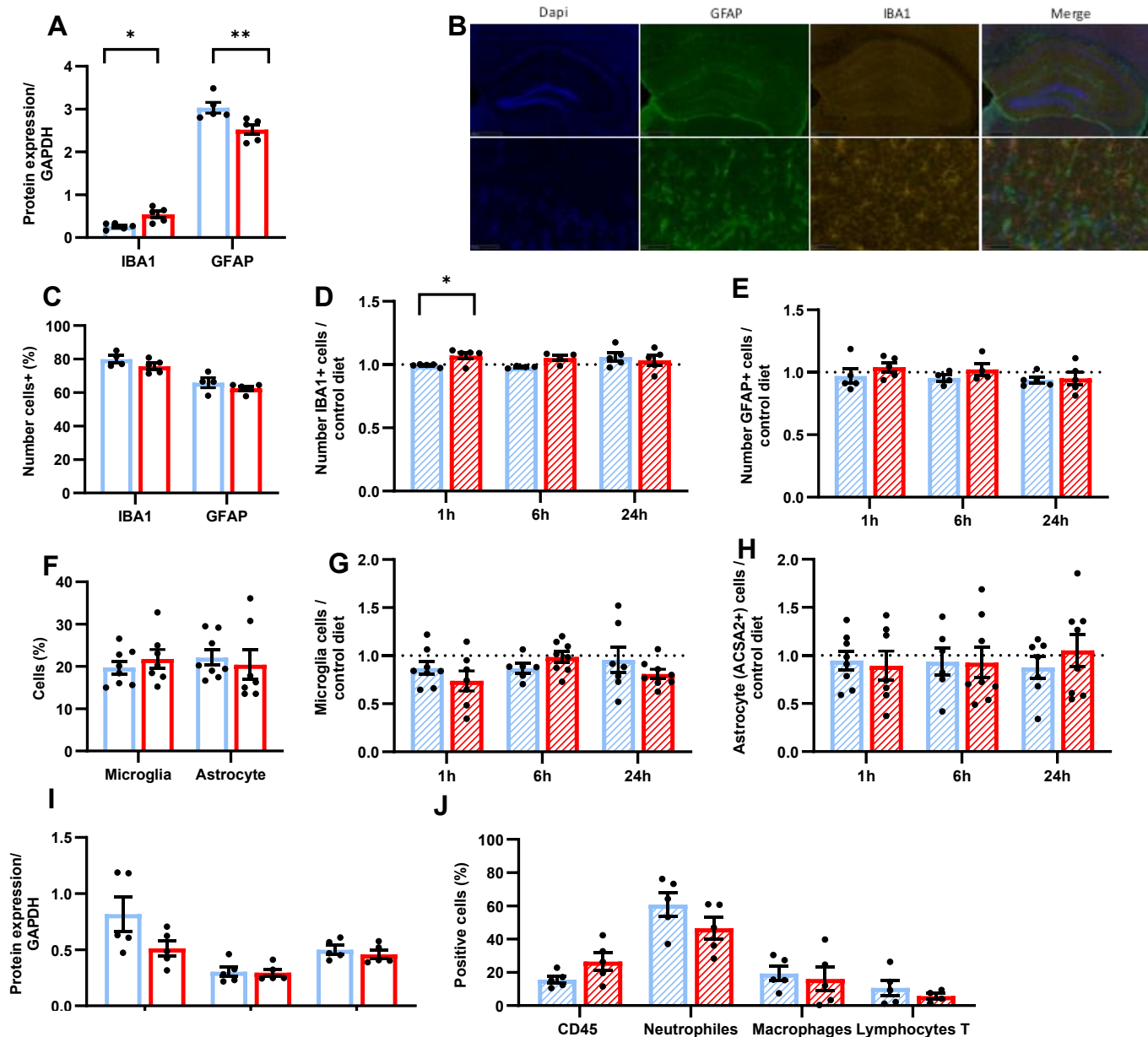


Supplemental 5. Ketoprofen treatment protects from POCD in obese animals.

ND- and HFD-fed mice treated with NaCl or Ketoprofen 1 h prior to the surgery and 24 h after the surgery. (A) the percentage of time spent at the displaced object as a preference index in the OL test ($n = 10$). (B) Plasma cytokine levels CXCL-10, IL-1 β , IL-6 measured 1 hour after surgery ($n = 5$). (C) total weight and (D) visceral or (E) subcutaneous ipsilateral and (F) contralateral adipose tissue weight ($n = 10$). (G) Hippocampal Representative western blot protein expression of (H) NeuN protein in control diet and (I) in surgery compared to control diet groups and (J) BDNF protein in control diet and (K) surgery compared to control diet groups 48 h after surgery ($n = 5$). (L) Hematoma collected at the site of surgery mRNA inflammatory genes ($n = 9$). NDs NaCl (Normal Diet surgery with NaCl) blue border and hatched pattern, NDs Ketoprofen (Normal Diet with surgery with Ketoprofen) black border and filed blue, HFDs NaCl (High Fat Diet with surgery with NaCl) red border and hatched pattern, HFDs Ketoprofen (High Fat Diet with surgery with Ketoprofen) black border and filed red.

Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using (A) Student's t -test compared to 50% and T tests (B-L).

Supplemental Figure S6

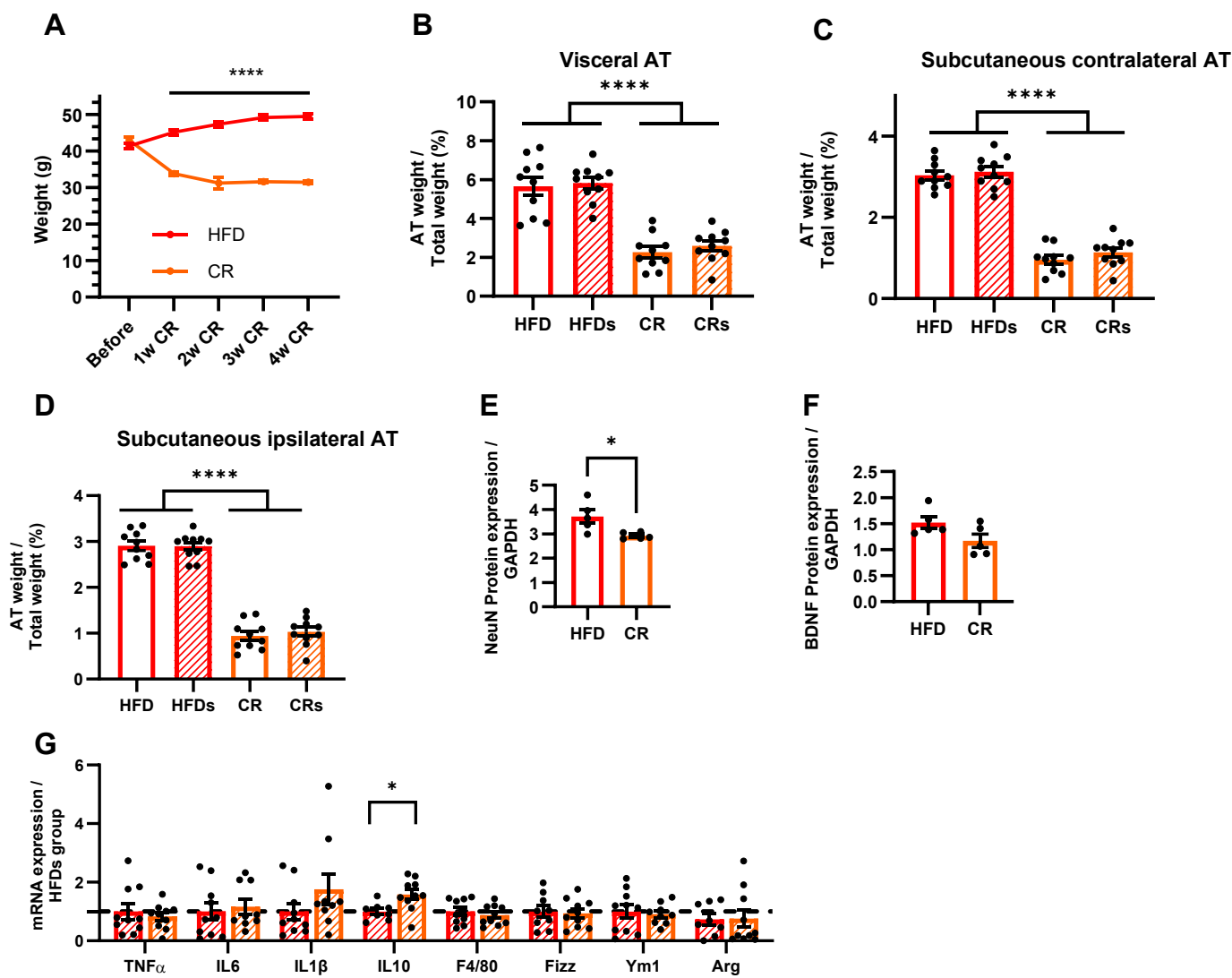


Supplemental 6. Obesity is associated with specific fracture-induced inflammatory responses.

(A) Quantification of western blot of basal protein level using IBA1 protein for microglia and GFAP protein for astrocytes. (B-E) Photomicrographic images of the nuclei (DAPI) and the indicated proteins and their quantification 1 h, 6 h, 24 h post-surgery: nucleus blue (DAPI), IBA1 red (microglia), GFAP green (astrocytes) and quantification of (C) control groups and (D-E) fractured mice ($n = 5$, Scale bar length 500 μ m and 50 μ m for zoomed image), (F-H) Flow cytometry measure of microglia (cd45low/cd11b) and astrocytes (acsa2) in (F) control group and (G-H) fractured mice 1 h, 6 h, 24 h post-surgery ($n = 5$). (I) Quantification of western blot of protein expression of tight junction Claudin 5, Occludin and Zonula Occludens 1 ($n = 5$). (J) Flow cytometry of hematoma percentage of immune cells ($n=5$).

ND (Normal Diet no surgery) bleu border, NDs (Normal Diet with surgery) bleu border and pattern, HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern. Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests (A-J).

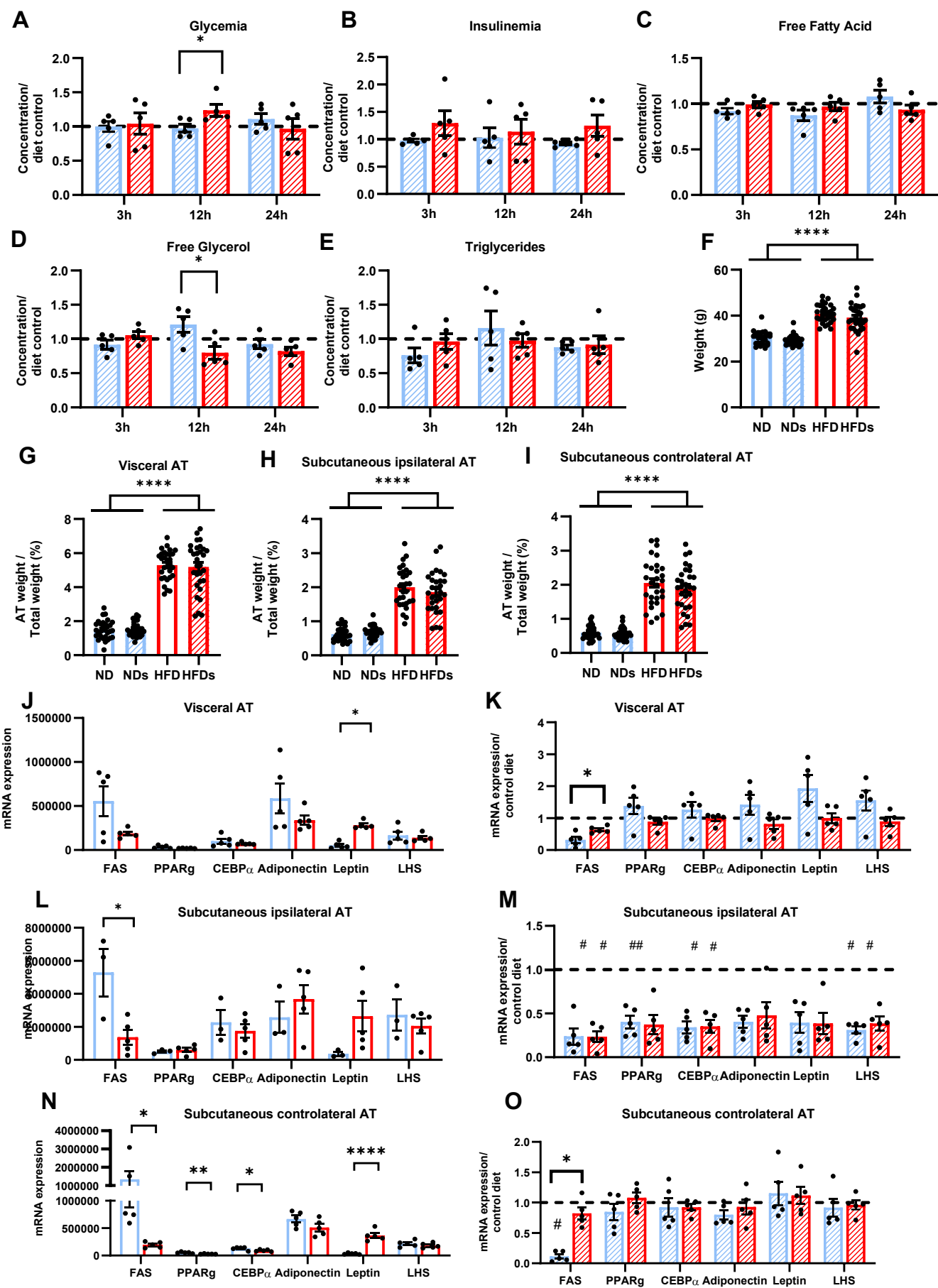
Supplemental Figure S7



Supplemental 7. Four weeks of caloric restriction prevents POCD in obese animals.

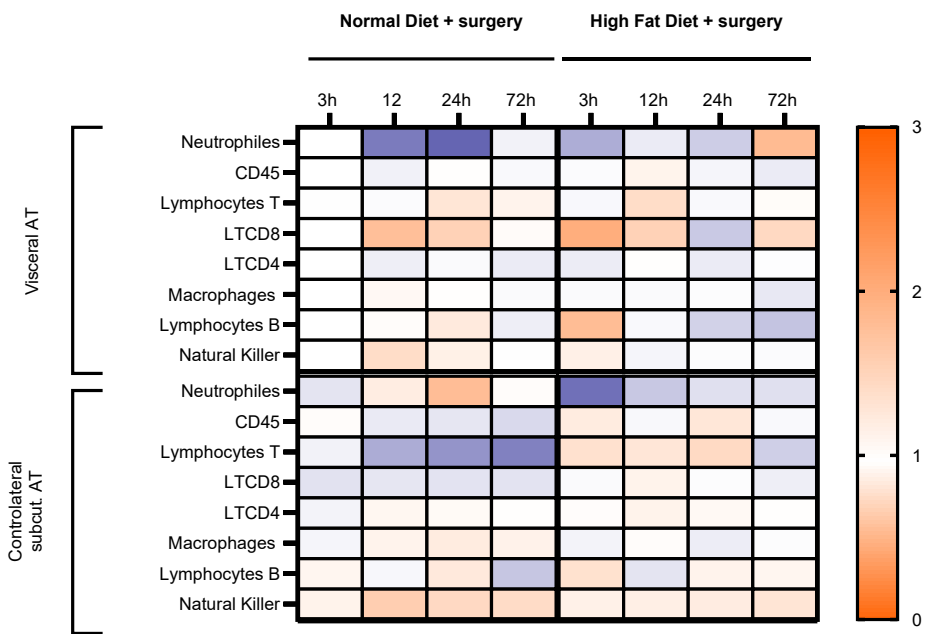
Obese mice subjected to 4 weeks of caloric restriction with normal diet after 8 weeks of high fat diet. (A) Animals' total weight measured each week before and after caloric restriction. (B) Visceral, (C) subcutaneous ipsilateral and (D) contralateral adipose tissue weight ($n = 10$). (E-F) Quantification of western blot protein expression of (E) NeuN and (F) BDNF in control diet groups. ($n = 5$). (G) mRNA levels of inflammatory genes in hematomas. HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern, CR (Caloric Restriction no surgery) orange border, CRs (Caloric Restriction with surgery) orange border and pattern. Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests (A-G).

Supplemental Figure S8

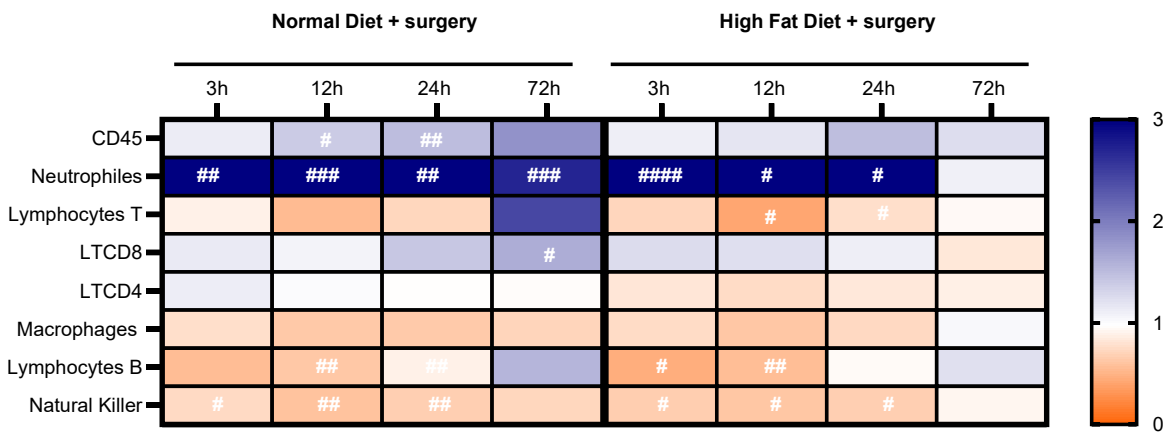


Supplemental Figure S8

P



Q

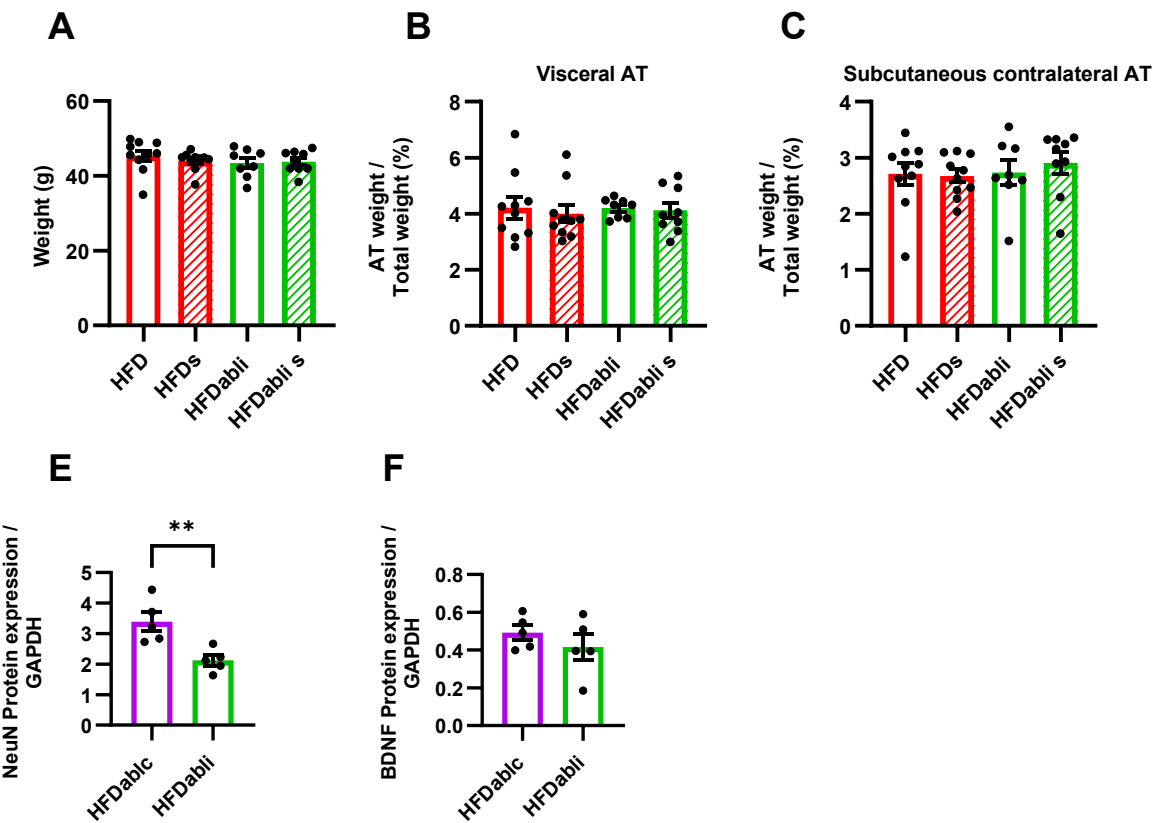


Supplemental 8. The effect of obesity on POCD is not due to metabolic or phenotypic major modification but to subcutaneous ipsilateral changes.

(A-E) Plasmatic measure of metabolic parameters compared to control diet groups 3 h, 12 h and 24 h post-surgery: (A) glycaemia, (B) insulinemia, (C) free fatty acid, (D) free glycerol, (E) triglyceride ($n = 5$). (F-I) phenotypic measure of (F) total body weight and (G) visceral, (H) subcutaneous ipsilateral and (I) subcutaneous contralateral white adipose tissue mass 72 hours post-surgery ($n = 15-17$). (J) mRNA gene expression of adipogenesis measured in subcutaneous ipsilateral adipose tissue in control diet groups ($n = 5$). (K) mRNA of adipogenesis pathways measured in subcutaneous ipsilateral adipose tissue 24 hours post-surgery ($n = 5$). (L) Flow cytometry immune cd45 positive cells measured in visceral and contralateral subcutaneous adipose tissue 3h, 12h, 24h and 72h after fracture. (M) Heatmap of immune cells of the stromal vascular fraction of subcutaneous ipsilateral adipose tissue 3h, 12h, 24h and 72h post-surgery ($n = 5$).

ND (Normal Diet no surgery) blue border, NDs (Normal Diet with surgery) blue border and pattern, HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern. Data are mean $\pm$ SEM. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$ analyzed using Student's t -tests comparing NDs and HFDs (A-K), # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$, #### $P < 0.0001$ analysed using Student's t -tests comparing ND to NDs or HFD to HFDs.

Supplemental Figure S9



Supplemental 9. Specific ablation of the subcutaneous ipsilateral adipose tissue prevents POCD in obese mice.

Obese mice subjected to either ipsilateral or contralateral subcutaneous adipose tissue whole ablation. (A) total weight, (B) visceral and (C) subcutaneous contralateral adipose tissue weight ($n = 10$). (E-F) Quantification of western blot protein expression of (E) NeuN and (F) BDNF in control diet.

HFD (High Fat Diet no surgery) red border, HFDs (High Fat Diet with surgery) red border and pattern, HFD ablation contralateral subcutaneous adipose tissue violet border, HFD ablation contralateral subcutaneous adipose tissue with surgery violet border and pattern, HFD ablation ipsilateral subcutaneous adipose tissue green border, HFD ablation ipsilateral subcutaneous adipose tissue with surgery green border and pattern.

Data are mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, analyzed using Student's t -tests (A-F).

Supplemental S10: Uncropped western blots

Figure 2C

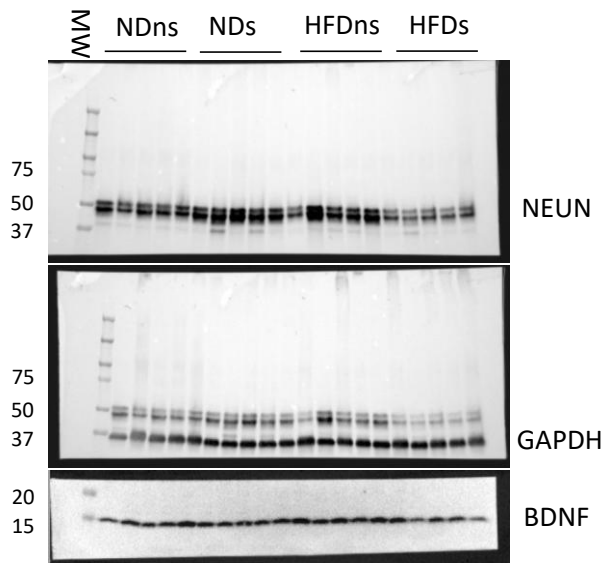


Figure 3C

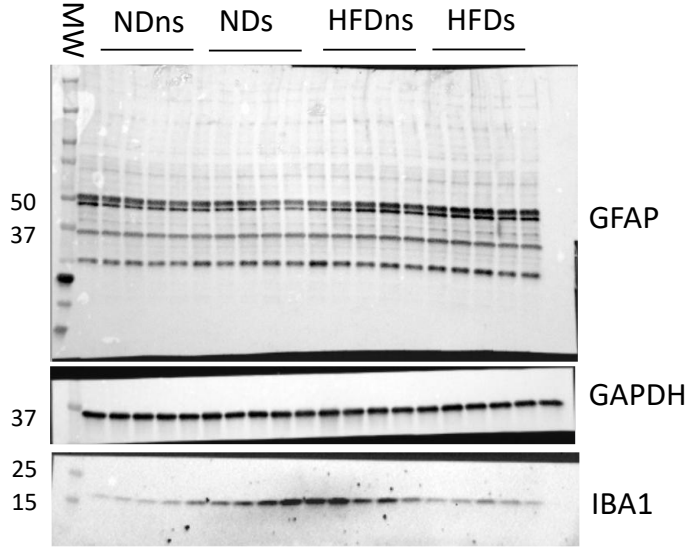


Figure 3F

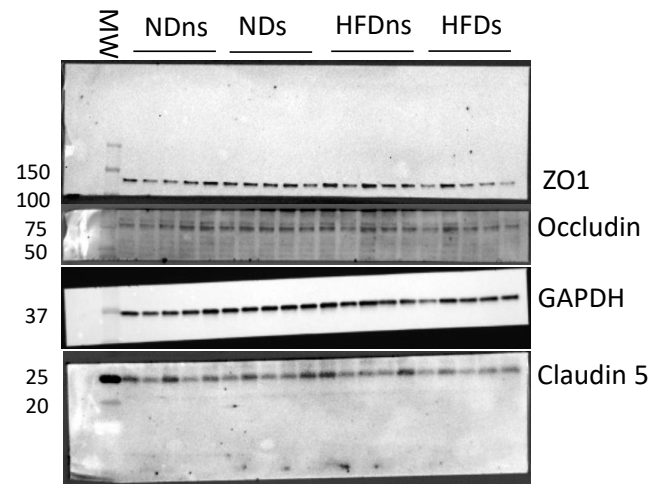
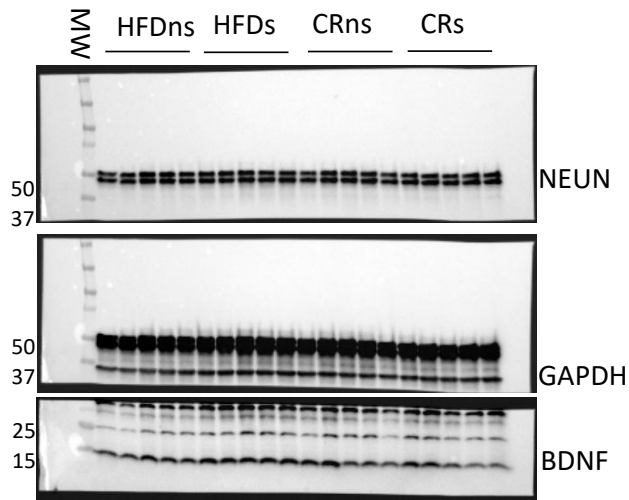
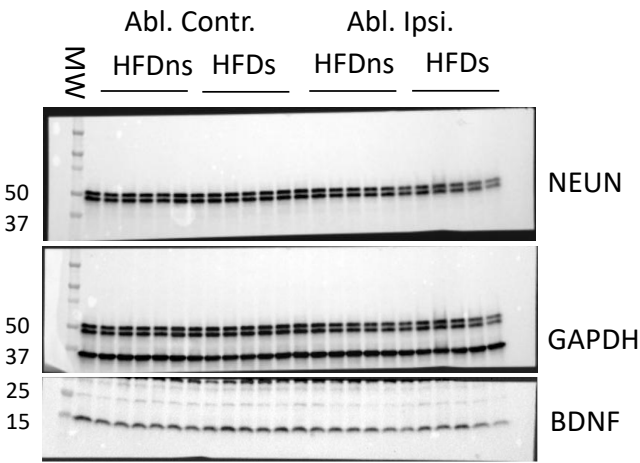


Figure 4F

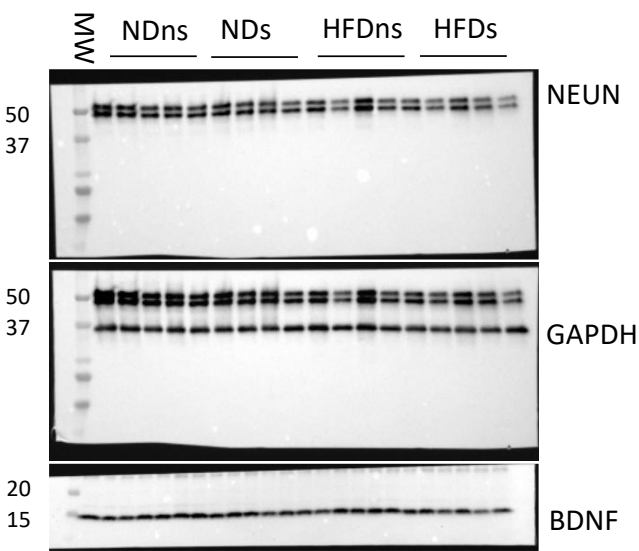


Supplemental S10: Uncropped western blots

Figure 5F



Supplemental Figure 4C



Supplemental Figure 5G

