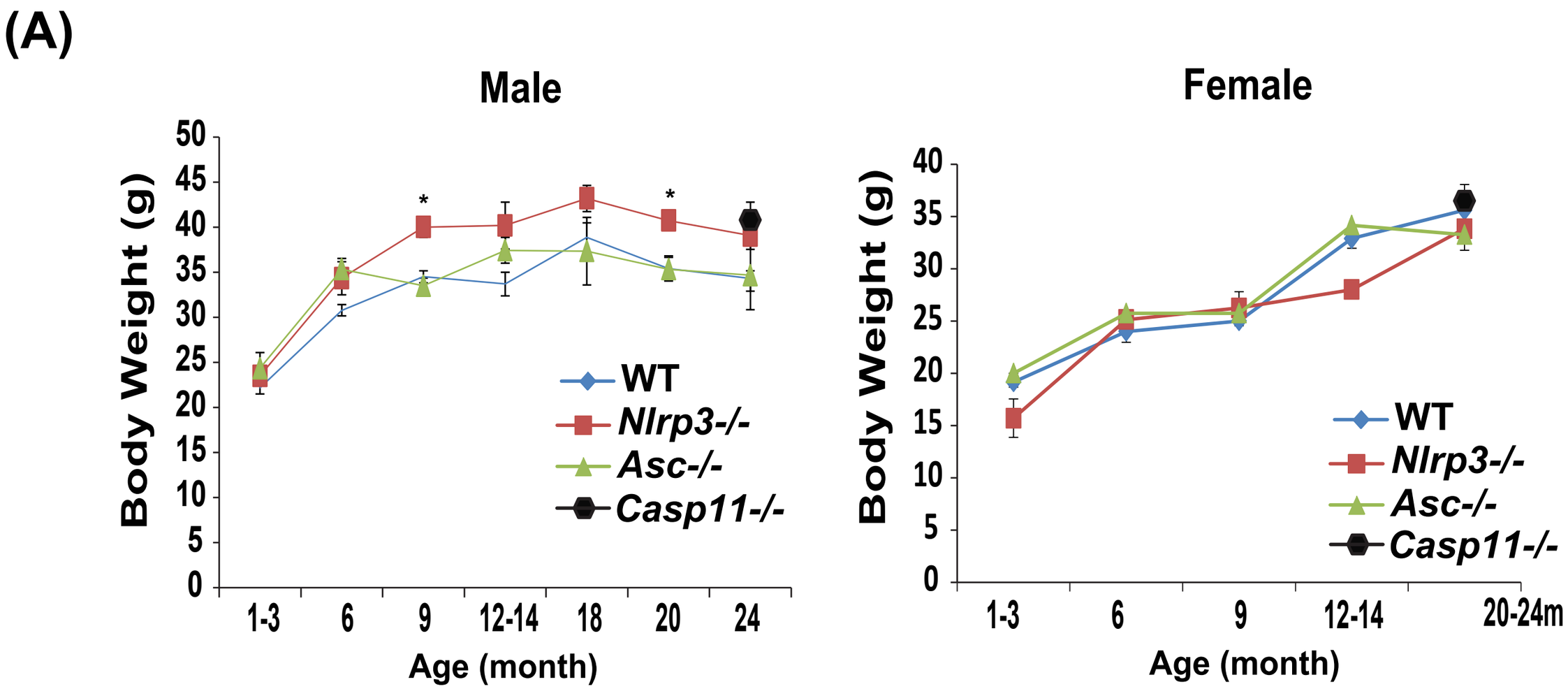


Figure S1, related to Figure 1: Deletion of canonical Nlrp3 inflammasome and non-canonical caspase-11 pathways does not induce adiposity. The body weights of (**A**) male and female WT, Nlrp3, Asc and Caspase-11 null mice fed normal chow diet till 2 years of age (n = 13-22/strain/age time point). (**B**) Representative hematoxylin and eosin stained section of livers of 23mo old WT and Nlrp3 deficient mice revealed no change in steatosis (n = 3/group). (**C**) Quantification of caspase-1 activation in adipose tissue. All data are presented as Mean (SEM)* P<0.05.

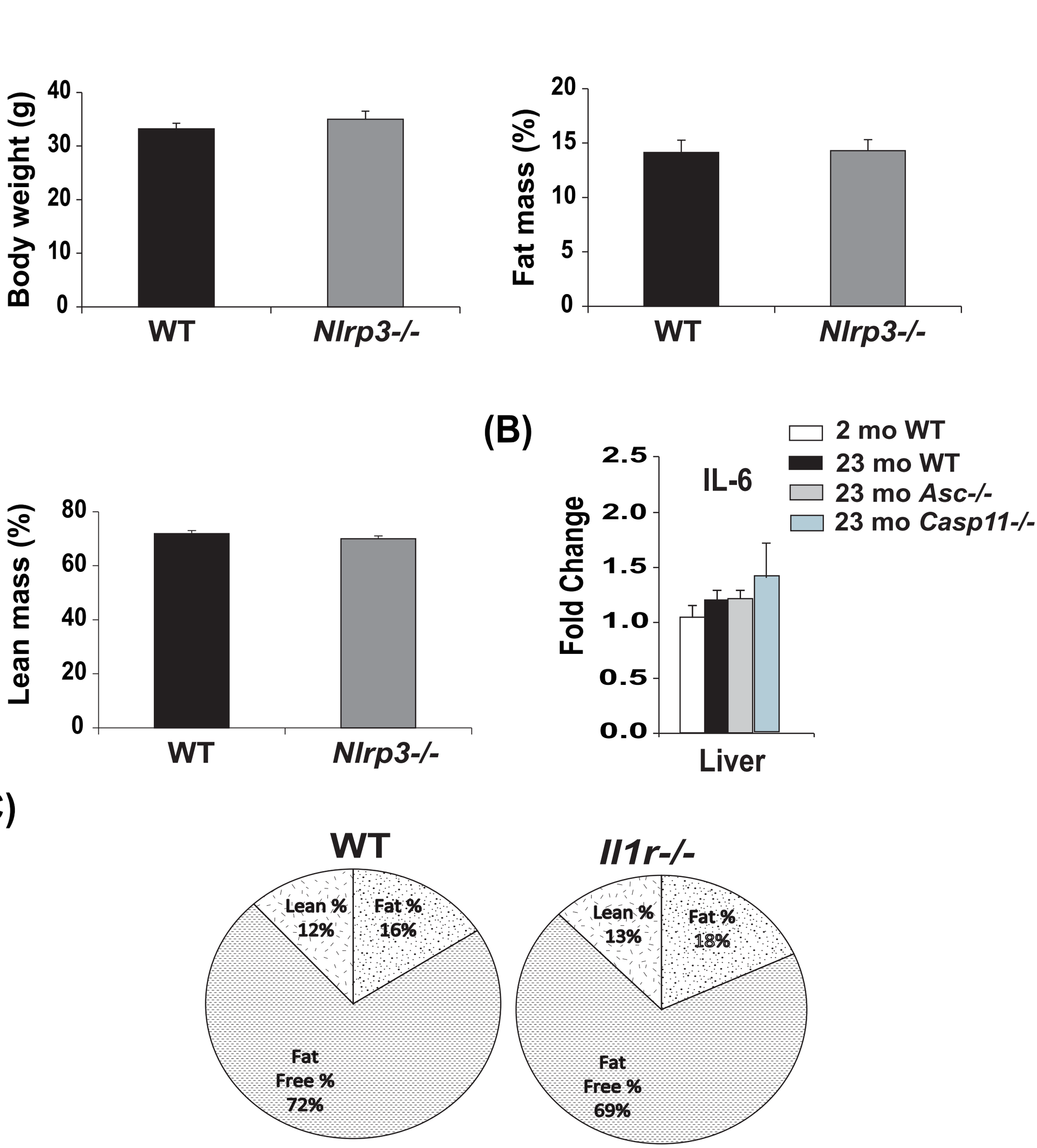


Figure S2, related Figure 1: Deletion of Nlrp3 and IL-1R does not impact body composition and hepatic IL-6 expression in aging mice. (A) The body composition (body weight, % lean, fat mass) was estimated by NMR in 24-month old male WT and *Nlrp3*$^{-/-}$ mice. (**B**) Real-time PCR analysis of IL-6 in liver of young and old WT, Asc and caspase-11 deficient mice. No significant change in IL-6 mRNA was observed in liver of these mice. (n = 4-6/strain). (**C**) Fat mass and lean mass was evaluated using NMR in 20month old WT and IL-1R mutant mice (n =12). All data are presented as Mean (SEM)* $P<0.05$.

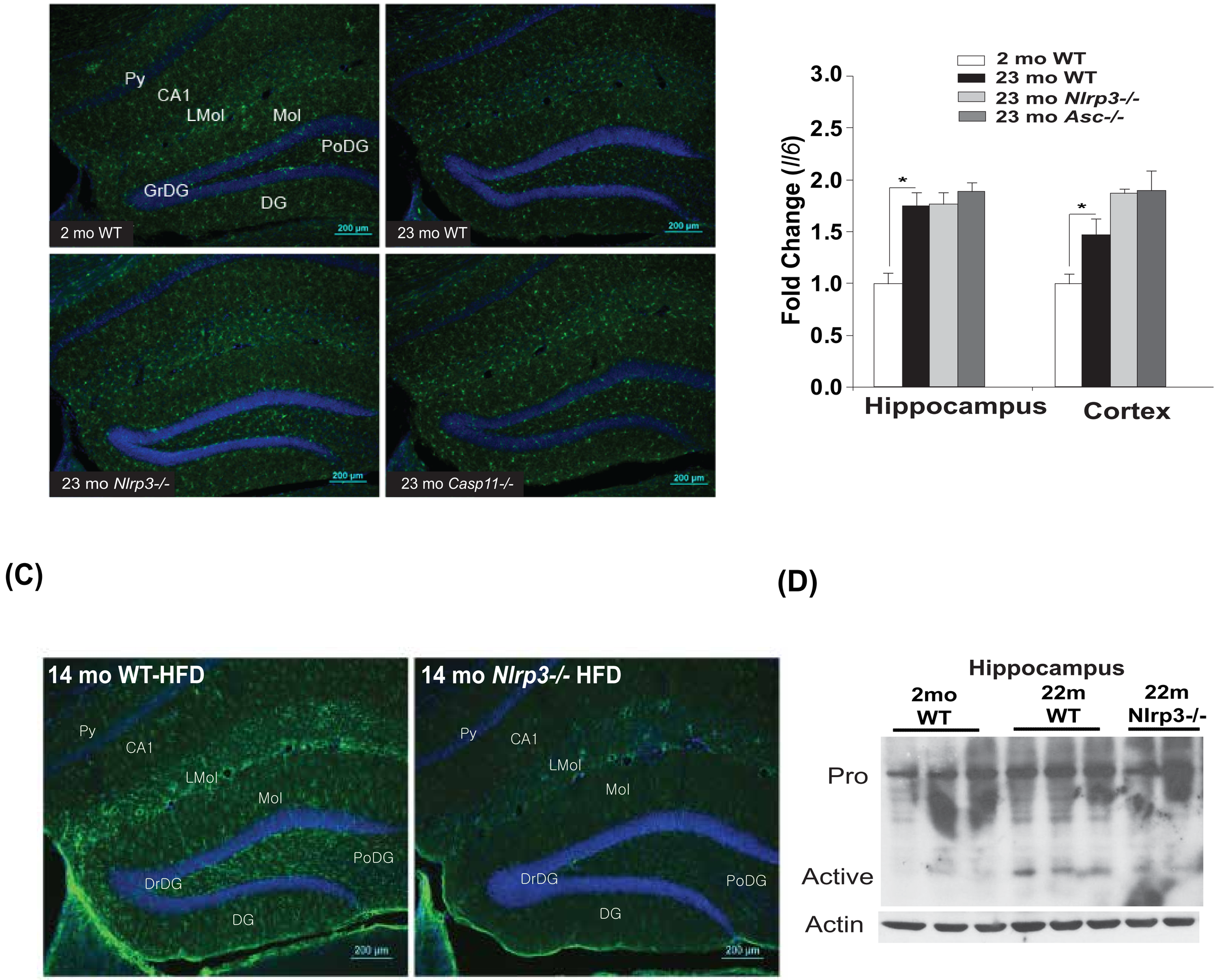
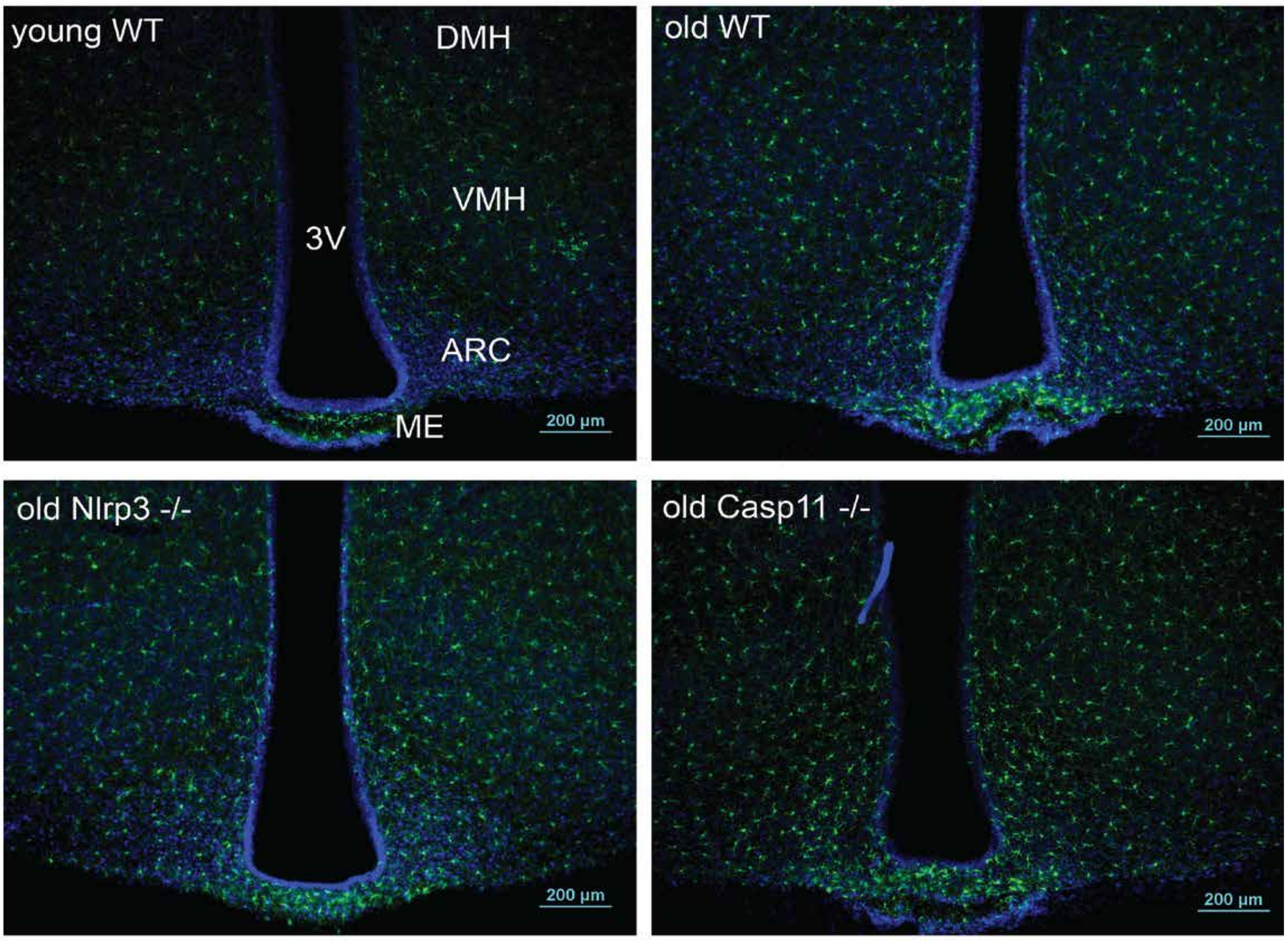


Figure S3, related Figure 3: **Impact of Nlrp3 inflammasome ablation on inflammation in hippocampus** (**A**) Brain cryosections from WT, Nlrp3 and caspase-11 mutant mice (23 month old) were stained with anti-Iba1 antibody to detect microglia. DG (dentate gyrus), Mol (molecular layer of DG) regions (n = 3). (**B**) Real-time PCR analysis of IL-6 in hippocampus and cortex of young and old WT, Asc and Nlrp3 deficient mice. Age-related increase in IL-6 mRNA expression was not modulated by loss of Nlrp3 or Asc. (n = 4-6/strain). (**C**) The WT, Nlrp3 mice were fed 60% HFD and aged for 14months. The brain cryosections were stained with anti-GFAP antibody. (**D**) The immunoblot analysis of IL-1β shows that compared to young WT mice there is an increase in active (p17 form) in hippocampus of 22m old WT mice which is attenuated in age-matched *Nlrp3*$^{-/-}$ animals. All data are presented as Mean (SEM)* $P<0.05$.

(A)



(B)

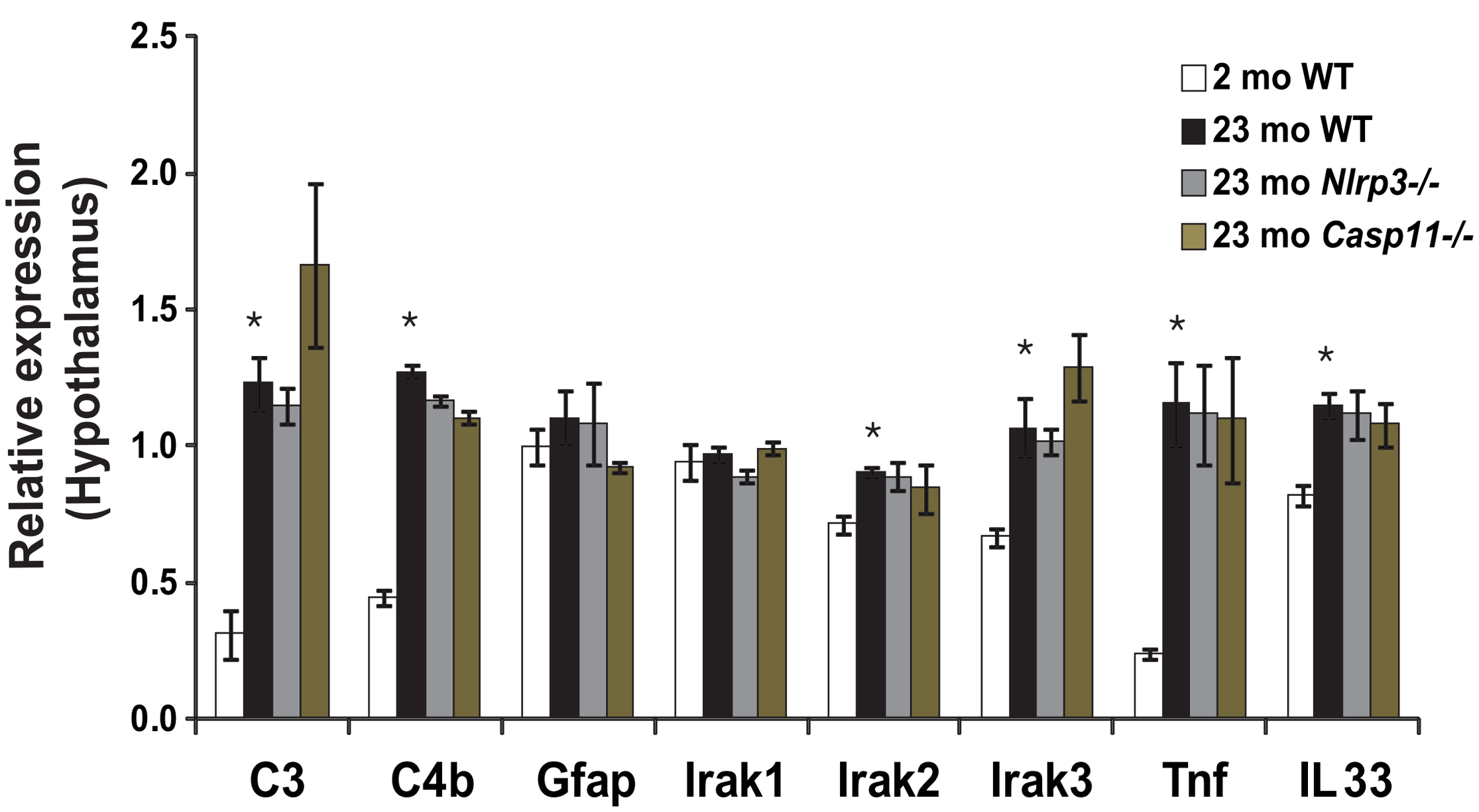


Figure S4, related Figure 3: **Nlrp3 and caspase-11 does not control age-related increase in hypothalamic inflammation. (A)** Brain cryosections from WT and Nlrp3 and caspase-11 mutant mice (23mo old) were stained with anti-Iba antibody-Alexa fluor 488 (green) to identify microglial morphology in dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), arcuate nucleus (ARC) and median eminence (ME) region of hypothalamus. (**B**) The realtime PCR analysis of major pro-inflammatory mediators that are elevated in hippocampus and regulated by Nlrp3 were analyzed in hypothalami of in young and old WT and Nlrp3 and caspase-11 deficient mice (n = 6-8/group). All data are presented as Mean (SEM)* $P<0.05$.

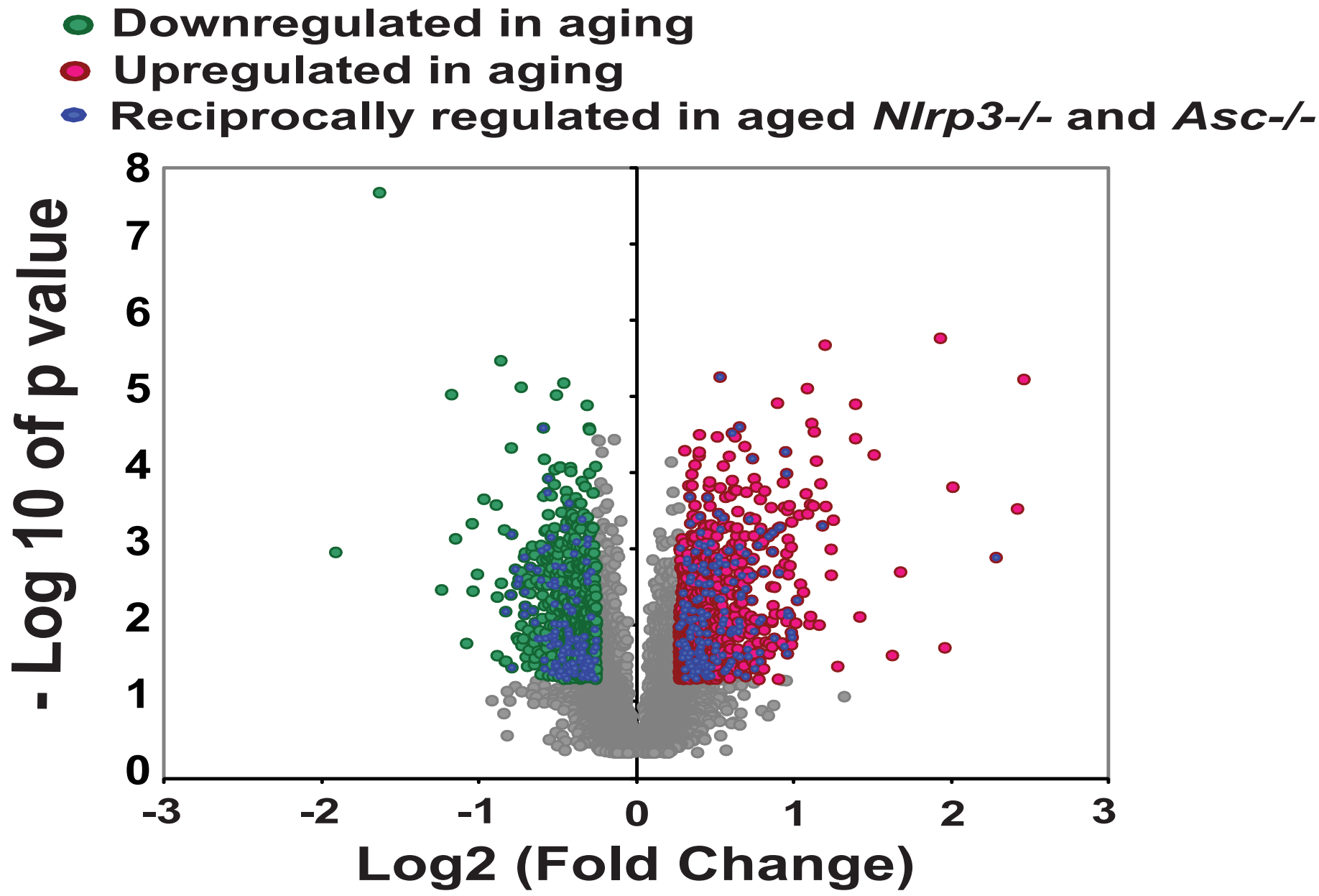


Figure S5, related Figure 4: Deletion of Nlrp3 and Asc protects against age-related alterations in transcriptome. Volcano plots of age-dependent gene expression differences in hippocampus in WT, *Nlrp3*$^{-/-}$ and *Asc*$^{-/-}$ mice. Grey color signifies gene probes that do not reach cutoff levels for statistical significance as well as fold change. Green color represents genes with decreased expression in old mice when compared to young;whereas, red color marks genes with increased expression in aged mice. The blue color overlay indicates gene probes where presence of either mutation prevents the age-dependent expression changes.

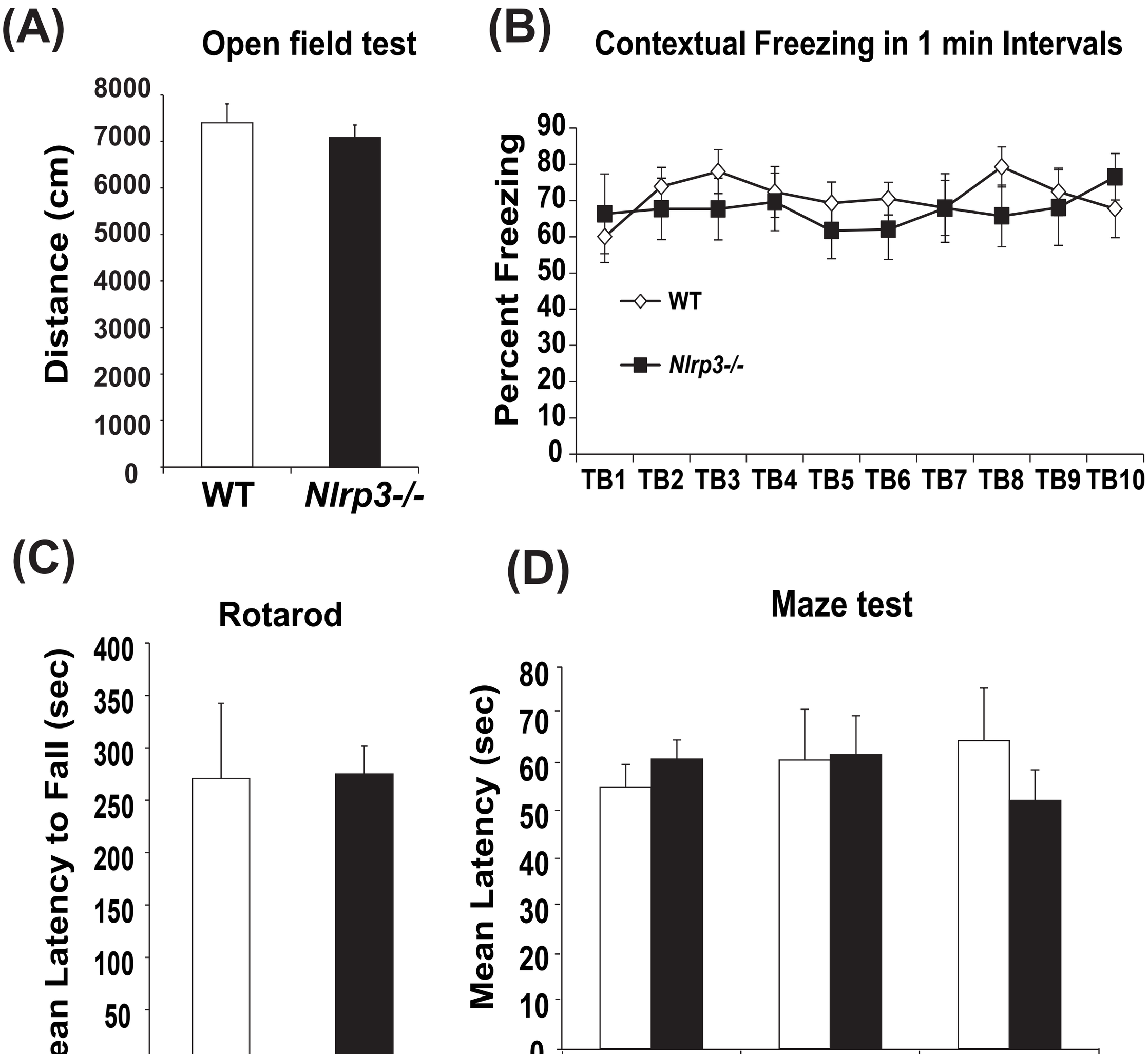


Figure S6, related Figure 7: The impact of canonical and noncanonical inflammasome on behavioral indices during aging. (**A**) Open Field Test of 18 month old female WT and *Nlrp3*$^{-/-}$ mice (**B**) Fear conditioning test, as measured by contextual freezing in 10 trial blocks in 18 month old female WT and *Nlrp3*$^{-/-}$ mice (**C**) The 18mo old WT and *Casp11*$^{-/-}$ mice were tested for motor performance by rotarod and (**D**) cognitive function in WT and Caspase-11 null mice was evaluated using Stone T-maze. They were given 15 trials in the T -maze with each trial having a maximum length of 300 sec. During each trial, the number of errors committed and the latency to reach the goal box were recorded. All data are presented as Mean (SEM)* $P<0.05$.

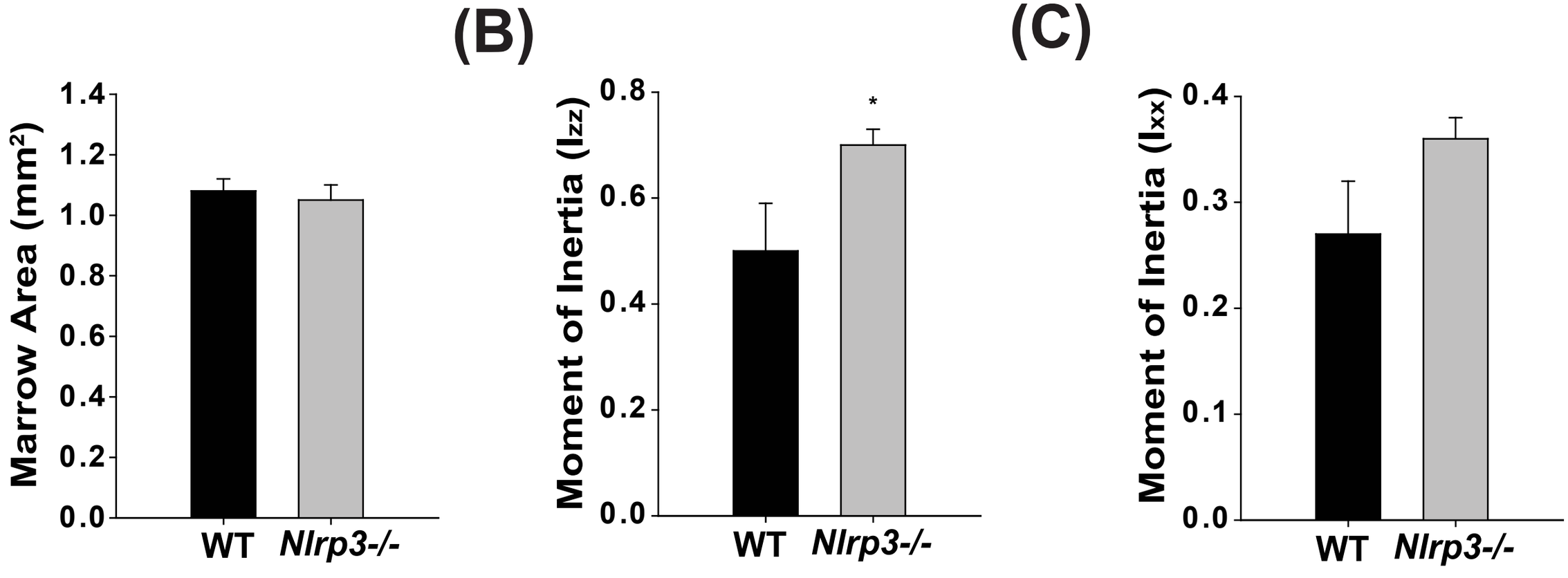


Figure S7, related Figure 7: Impact of Nlrp3 deletion on bone parameters during aging. The female WT and *Nlrp3*$^{-/-}$ mouse femurs were imaged by microcomputed tomography and analyzed for standard bone parameters (**A**) marrow area (**B, C**) momentia of inertia along x and z axes. (**D**) No difference in inner endochondrial perimeter or (**E**) outer periosteal perimeter were apparent ruling out the possibility of osteopetrosis in femurs of *Nlrp3*$^{-/-}$. All data are presented as Mean (SEM)* $P<0.05$.

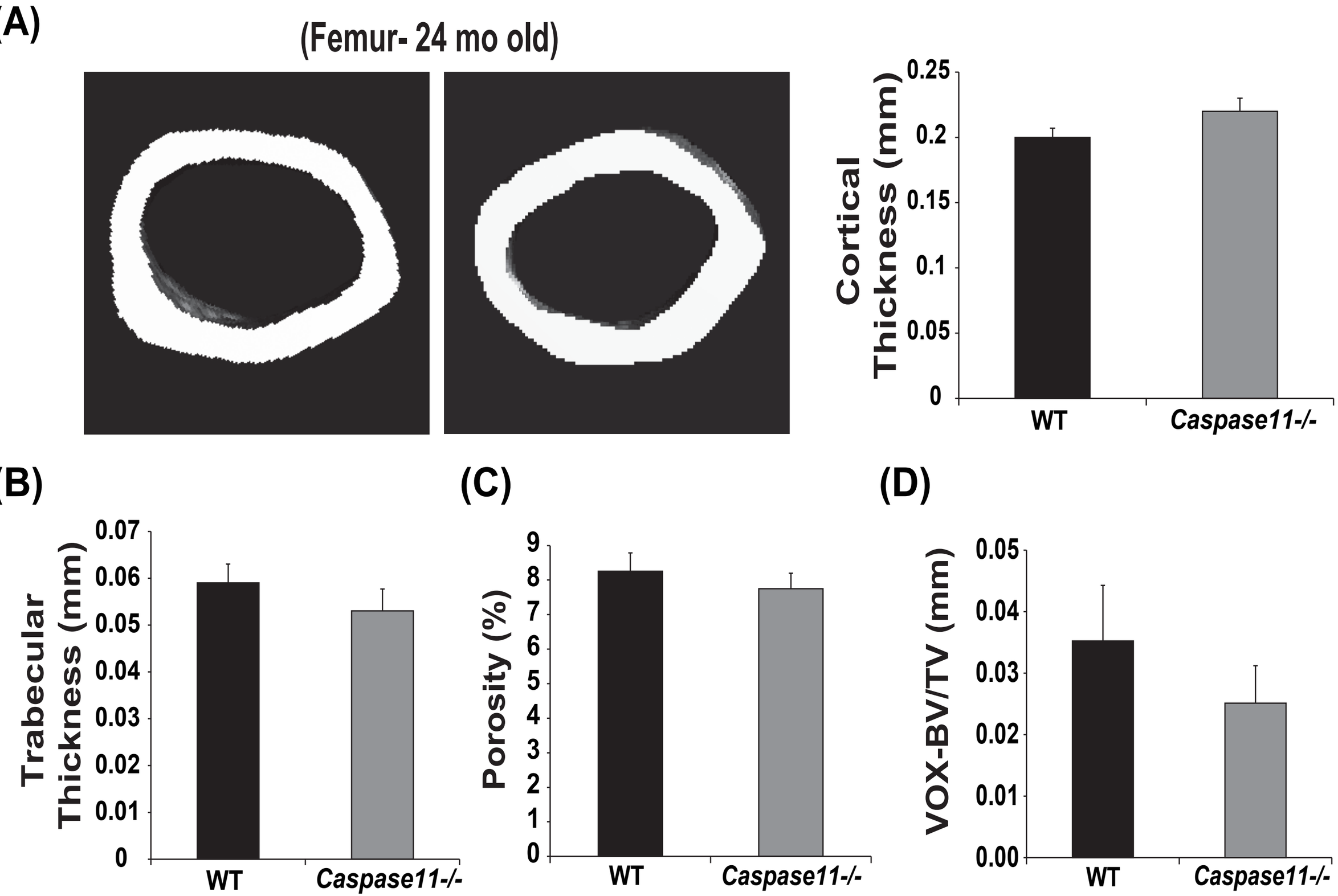


Figure S8, related Figure 7: Caspase-11 non canonical inflammasome does not protect against age-related changes in bone mass.

The female WT and *Casp11*$^{-/-}$ mouse femurs were imaged by microcomputed tomography and analyzed for (**A**) cortical thickness (**B**) trabecular thickness (**C**) porosity and (**D**) relative bone volume. All data are presented as Mean (SEM)* $P<0.05$.

Summary of Graphical Abstract: Hypothetical model of canonical Nlrp3 inflammasome as a major regulator of age-related inflammation and associated chronic diseases. Age related activation of NFkB may provide the priming 'signal 1' to induce increase transcription of IL1β and IL-18. Age related DAMPs such as ATP derived from necrotic cells, uric acid, lipotoxic fatty acids etc. serve as secondary signal to activate the Nlrp3 inflammasome leading to caspase-1 activation. The caspase-11 which serves a major sensor of PAMPs is not engaged during healthy aging. IL-1 mediates in part the age-related increase in frailty deficits in cognition. Upstream inhibition of Nlrp inflammasome in aging lowers age-related inflammation and degenerative changes in multiple organs.

Figure S1, related to Figure 1: **Deletion of canonical Nlrp3 inflammasome and non-canonical caspase-11 pathways does not induce adiposity.**

Figure S2, related Figure 1: Deletion of Nlrp3 and IL-1R does not impact body composition and hepatic IL-6 expression in aging mice.

Figure S3, related Figure 3: **Impact of Nlrp3 inflammasome ablation on inflammation in hippocampus.**

Figure S4, related Figure 3: **Nlrp3 and caspase-11 does not control age-related increase in hypothalamic inflammation.**

Figure S5, related Figure 4: Deletion of Nlrp3 and Asc protects against age-related alterations in transcriptome.

Figure S6, related Figure 7: The impact of canonical and noncanonical inflammasome on behavioral indices during aging.

Figure S7, related Figure 7: Impact of Nlrp3 deletion on bone parameters during aging.

Figure S8, related Figure 7: Caspase-11 non canonical inflammasome does not protect against age-related changes in bone mass.

Supplementary Table 1, related Figure 1, 3, 5 and 6: Primers pairs used for real-time-PCR analyses.

	Forward	Reverse
36B4	CAC TGG TCT AGG ACC CGA GAA	AGG GGG AGA TGT TCA GCA TGT
Bdnf	5'-AGA AGG TTC GGC CCA ACG AAG AAA-3'	5'-GAC ATG TTT GCG GCA TCC AGG TAA-3'
C1qa	5'-GAA AGG CAA TCC AGG CAA TA-3'	5'-CTG GTT GGT GAG GAC CTT GT-3'
C1qb	5'-ACT TCC GCT TTC TGA GGA CA-3'	5'-GAC CTC ACC CCA CTG TGT CT-3'
C3	5'-AAG CAT CAA CAC ACC CAA CA-3'	5'-CTT GAG CTC CAT TCG TGA CA-3'
C4b	5'-GAG GAG GCA GAA CTC ACG TC-3'	5'-GAA CGT TGG AGG CTT CAG AG-3'
GAPDH	5'-TCA ACA GCA ACT CCC ACT CTT CCA-3'	5'-ACC CTG TTG CTG TAG CCG TAT TCA-3'
Gbp2	5'-AAG AGC CTG GTG CAG ACC TA-3'	5'-TTG CAC TGC TGC TGA GTT CT-3'
Gfap	5'-ACA AGG ACG TGG TGA TGT GA-3'	5'-CAG AAG GAA GGG AAG TGC TG-3'
Id2	5'-CAT CCC ACT ATC GTC AGC C-3'	5'-ATT CGA CAT AAG CTC AGA AGG G-3'
Id3	5'-AGC TTT TGC CAC TGA CCC-3'	5'-AGA TCG AAG CTC ATC CAT GC-3'
Ifit3	5'-GTG GTG GAT TCT TGG CAG TT-3'	5'-GAC ACA CTT CCG GTT GTC CT-3'
IL-10	5'-GGG TTG CCA AGC CTT ATC GGA AAT-3'	5'-TCT TCA GCT TCT CAC CCA GGG AAT-3'
IL-18	5'-CGA CTT CAC TGT ACA ACC GCA GTA-3'	5'-CAC AGC CAG TCC TCT TAC TTC ACT-3'
IL-1b	5'-AAG AGC TTC AGG CAG GCA GTA TCA-3'	5'-ATG AGT CAC AGA GGA TGG GCT CTT-3'
IL-33	5'-GGC TGC TTG CTT TCC TTA TG-3'	5'-CCG TTA CGG ATA TGG TGG TC-3'
IL-6	5'-AGA CAA AGC CAG AGT CCT TCA GAG-3'	5'-TTG GTC CTT AGC CAC TCC TTC TGT-3'
Irak1	5'-TCT GCC TCC ACC TTC CTC-3'	5'-CTC TGG GCT TGA CTT GGT G-3'
Irak2	5'-TGT CAC CTG GAA CTC TAC CG-3'	5'-TTT CTC CTG TTC ATC CTT GAG G-3'
Irak3	5'-GGA GAA GGG GAG ATA TTC GAA G-3'	5'-GTG ACG GAA CAG GAG TAG AAC-3'
Map2k7	5'-GTC CCA TTG TCC TGC AGT TT-3'	5'-AAC TTT GGT GCT GGG ATT TG-3'
Symn	5'-CTG ACC CGT GTG TGT TTC AC-3'	5'-TTT CCA TTC AAA TCC GCT TC-3'
Tab2	5'-ACA TTC AGC ATC TCA CAG ACC-3'	5'-TCT TTG AAG CCG TTC CAT CC-3'
Tnc	5'-GAG AAG GGC AGA CAC AAG AG-3'	5'-GAC AAA GTA CTC ATA GGC CAG G-3'
Tnf	5'-ACG GCA TGG ATC TCA AAG ACA ACC-3'	5'-TGA GAT AGC AAA TCG GCT GAC GGT-3'
Trib2	5'-CCC GAC TGT TCT ACC AGA TTG-3'	5'-AAG CGT CTT CCA AAC TCT CC-3'