Supplemental Information

Obesity Challenges the Hepatoprotective Function of the Integrated Stress Response to Asparaginase Exposure in Mice

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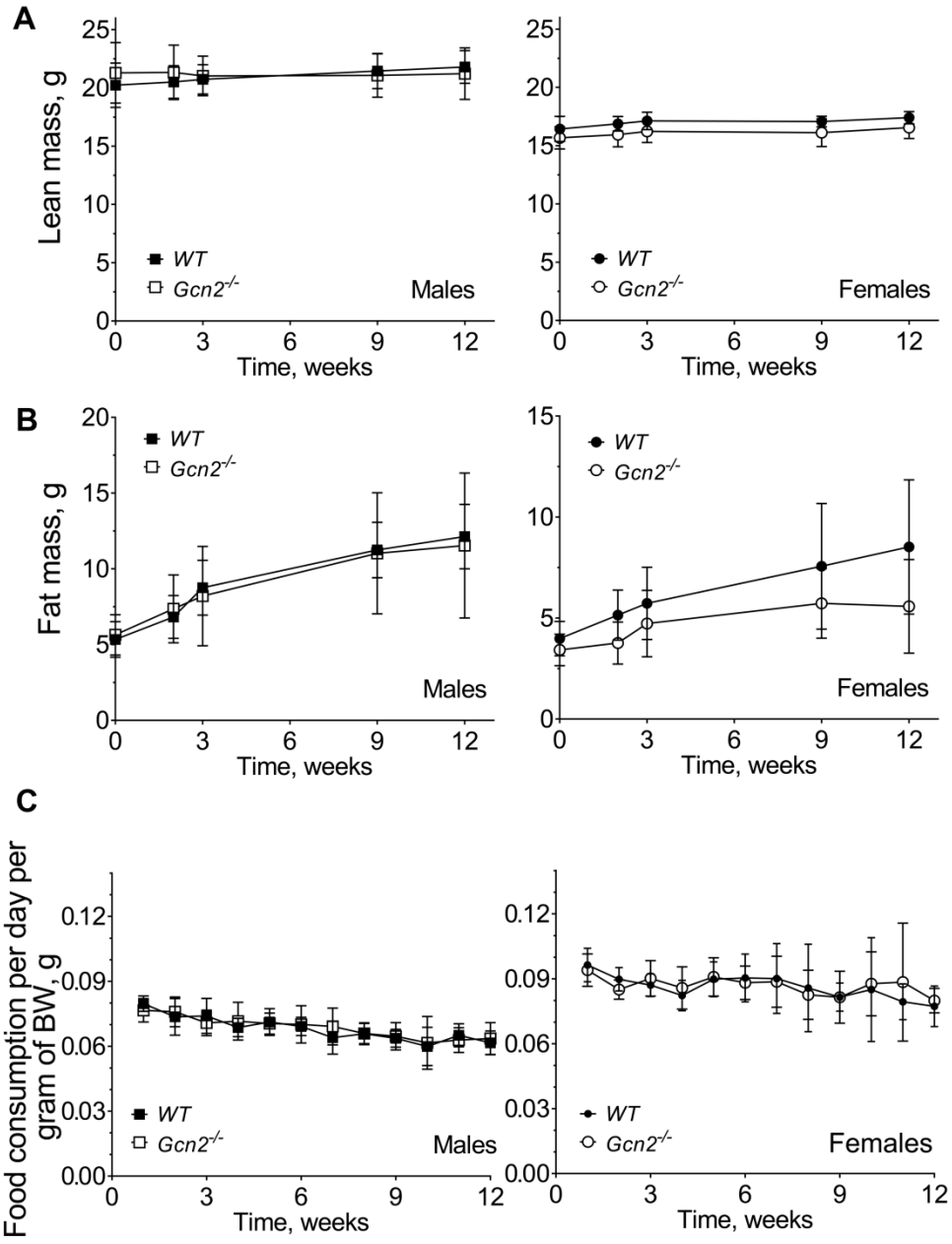
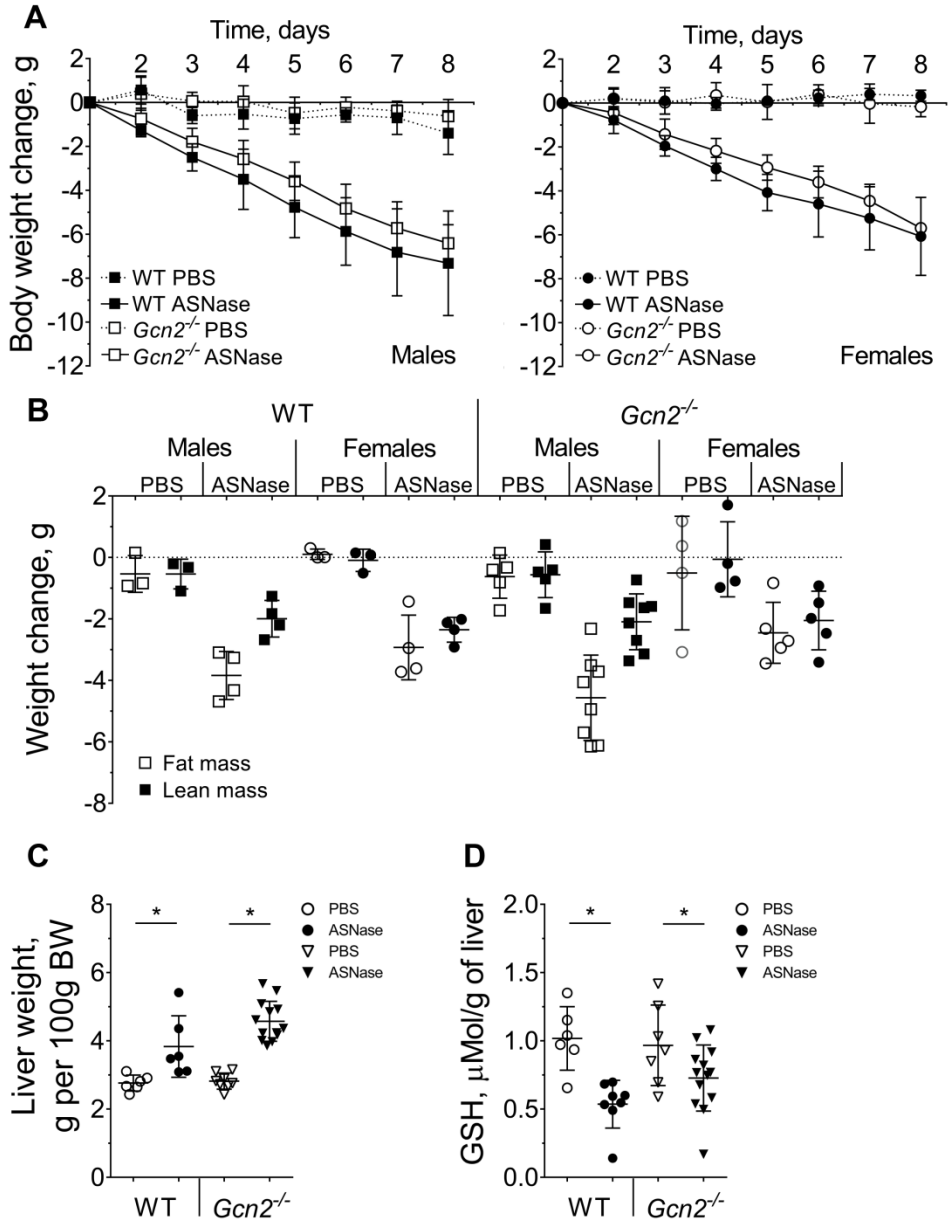
Figure S1: WT and *Gcn2*$^{-/-}$ animals before ASNase treatment (body composition / food intake)



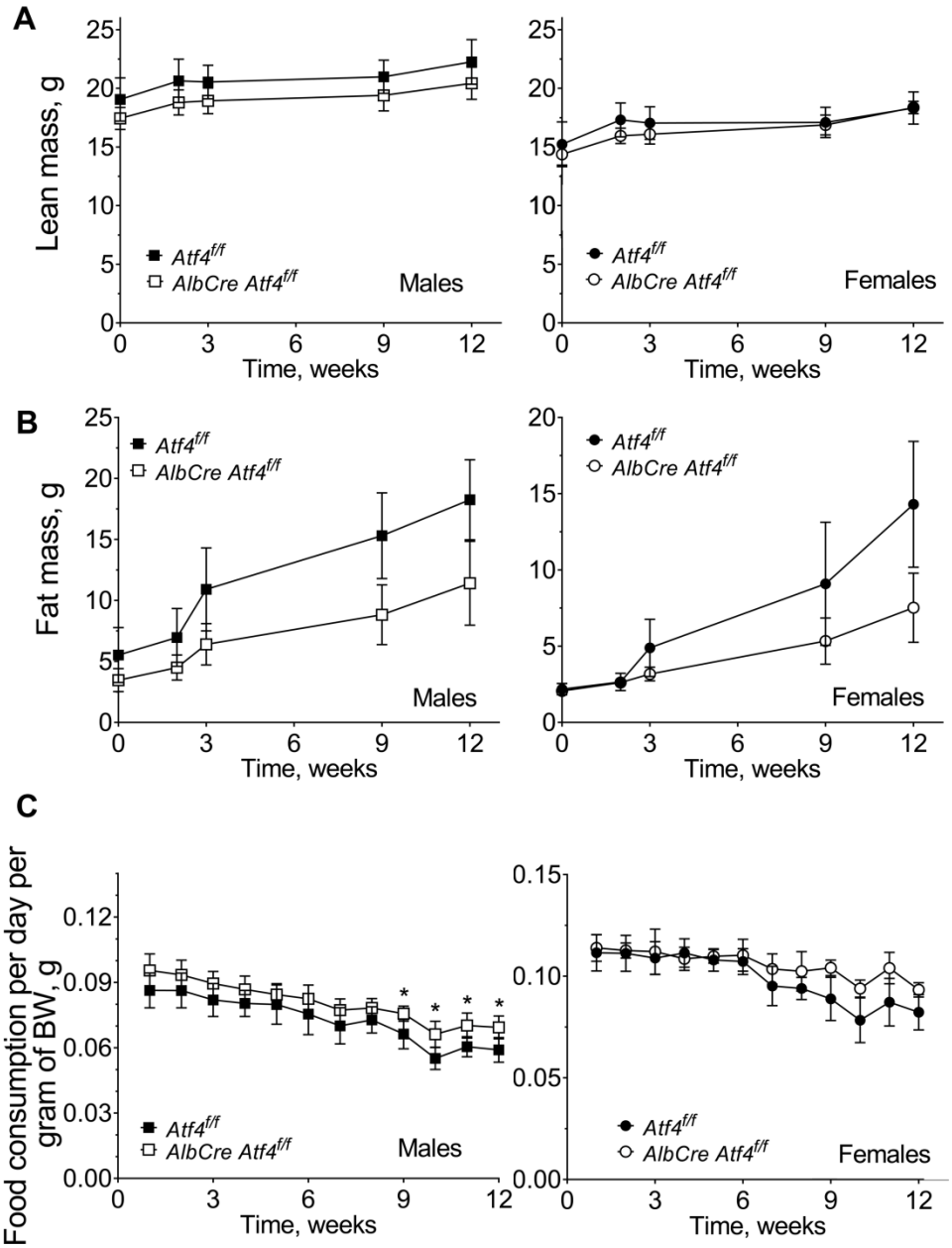
(A-B) Body composition during preconditioning phase of the obesogenic diet was assessed by MRI. Animals maintained lean mass at a relatively stable level (A) and gained mostly fat mass (B). (C) Food intake measured during preconditioning phase of the study. Data are represented as means ± SD. * $p < 0.05$.

Figure S2: WT and *Gcn2*$^{-/-}$ animals post-ASNase treatment (body weight / composition / liver weights / GSH)



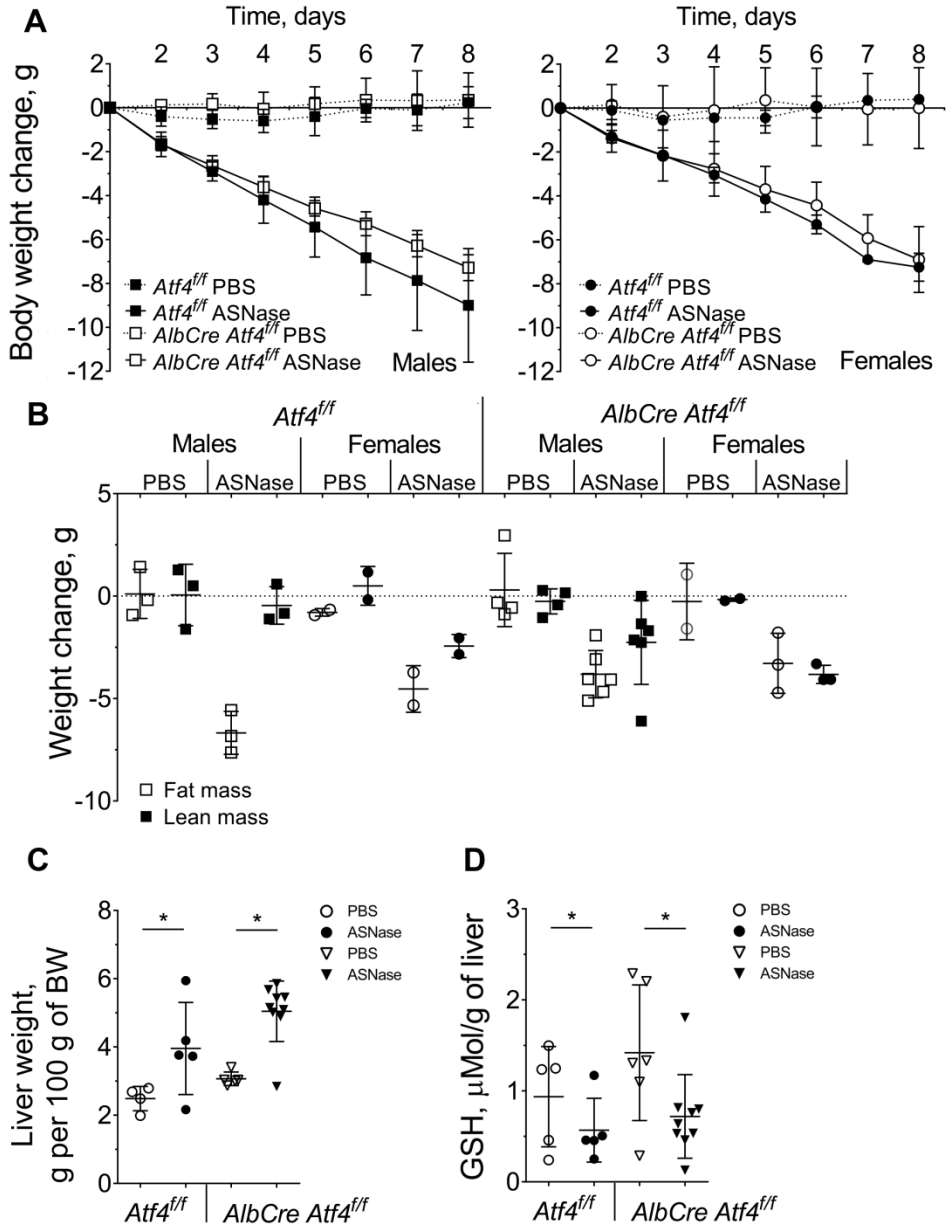
(A) Weight loss during asparaginase treatment in males (left) and females (right). (B) Post treatment analysis of body composition by MRI. (C) Liver weights from the obese animals expressed as percentages of body weight. (D) Hepatic glutathione levels in obese WT and *Gcn2*$^{-/-}$ animals post-treatment. Data are represented as means ± SD. * $p < 0.05$.

Figure S3: Wild type (*Atf4*$^{f/f}$) and *AlbCre Atf4*$^{f/f}$ animals before ASNase treatment (body composition / food intake)



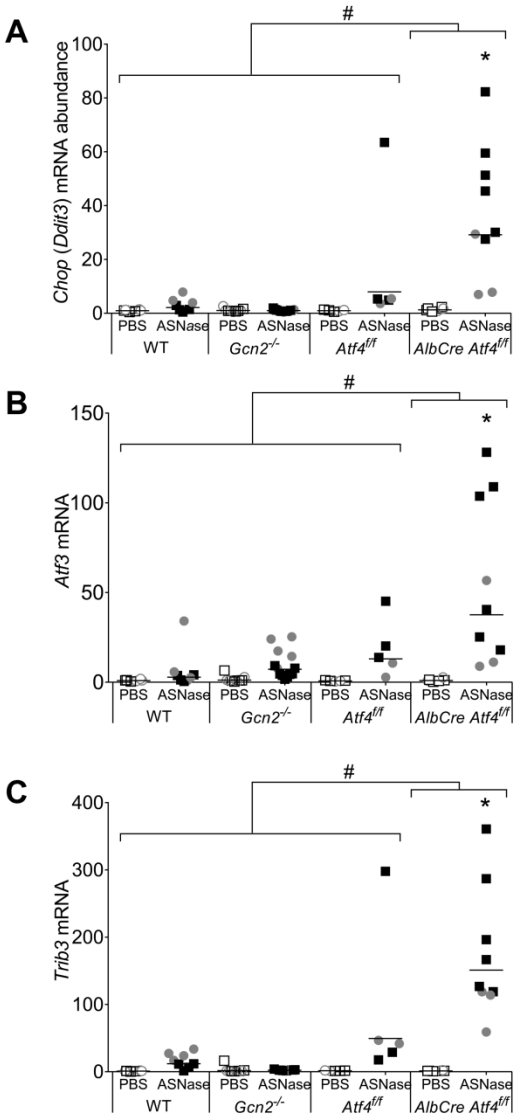
(A-B) Body composition during preconditioning phase of the obesogenic diet feeding was assessed by MRI: lean mass for males (left) and females (right), fat mass for males (left) and females (right). (C) Food intake measured during preconditioning phase of the study. Data are represented as means ± SD. * $p < 0.05$.

Figure S4: Wild type (*Atf4$^{f/f}$*) and *AlbCre Atf4$^{f/f}$* animals post-ASNase treatment (body weight / composition / liver weights / GSH)



(A) Weight loss during asparaginase treatment in males (left) and females (right). (B) Post treatment analysis of body composition by MRI. (C) Liver weights from the obese animals expressed as percentages of body weight. (D) Hepatic glutathione levels in obese WT and *Gcn2*$^{-/-}$ animals post-treatment. Data are represented as means ± SD. * $p < 0.05$.

Figure S5. Hepatic *Chop*, *Atf3*, *Trib3* gene expression across the strains



Visualization of heterogeneous expression of *Chop*, *Atf3* and *Trib3* genes for all the analyzed subjects (males are shown in squares, females are shown in circles, open markers represent control PBS-treated animals, filled markers represent asparaginase-treated animals). No obvious sexual dimorphism in transcriptional response was observed. Transcriptional induction of these genes in *AlbCre Atf4*$^{f/f}$ strain was significantly different from all other strains as marked by an asterisk. Horizontal marks represent geometric means.

Horizontal bars indicate mean values.

* marks $p < 0.05$.

marks difference between strains ($p<0.05$).