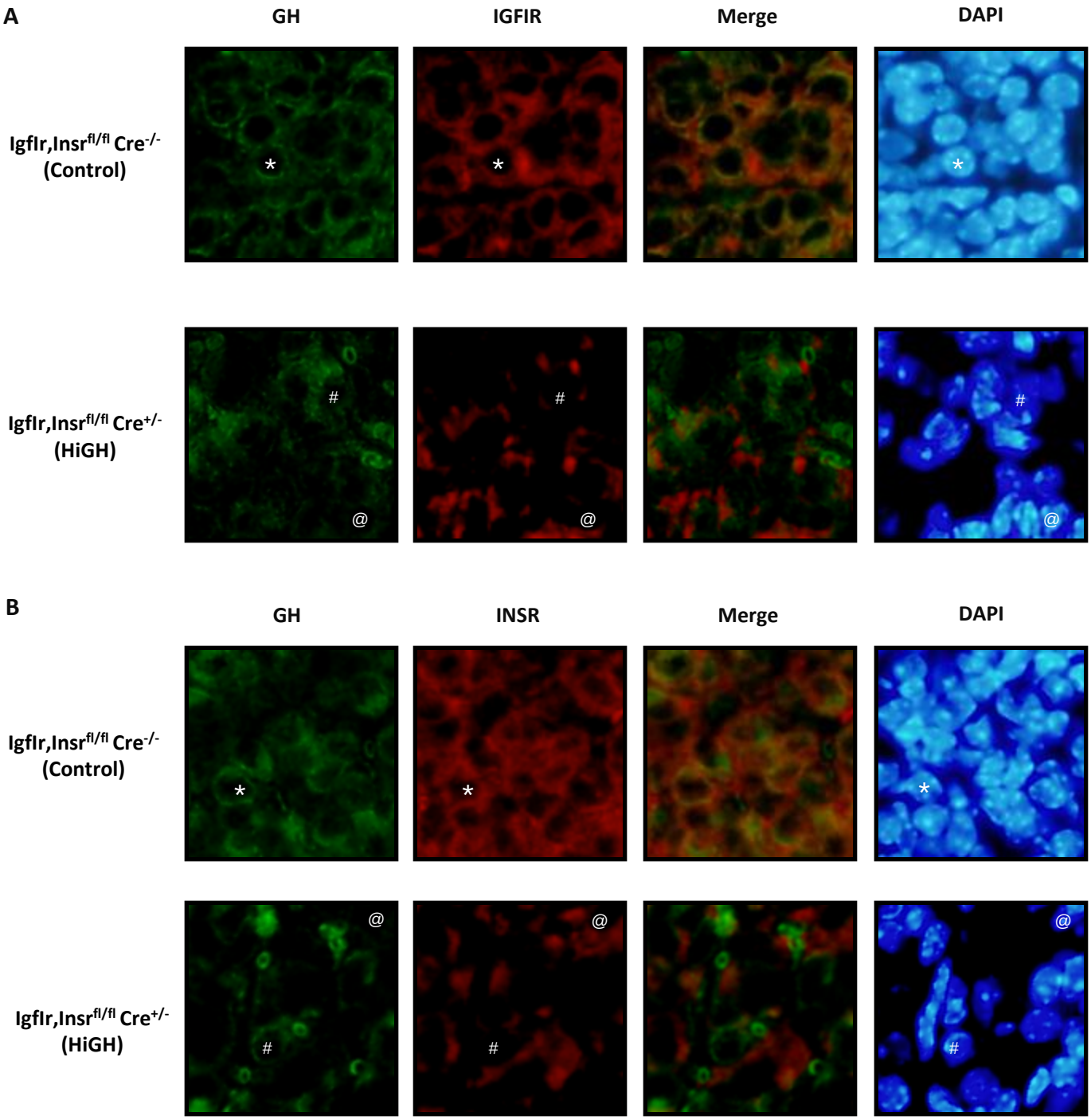

Fig. S1. Confirmation of IGFIR and INSR deletion from GH-producing cells in IgfIr,Insr$^{fl/fl}$ Cre$^{+/-}$ (HiGH) mice by double immunohistochemistry with GH and IGFIR or INSR antibodies, visualized with fluorescence labeled secondary antibodies. 5-µm paraffin sections of control (IgfIr,Insr$^{fl/fl}$ Cre$^{-/-}$) and IgfIr,Insr$^{fl/fl}$ Cre$^{+/-}$ (HiGH) mouse pituitaries were simultaneously incubated with anti-GH (green, A and B) and anti-IGFIR (red, A) or anti-INSR (red, B) and nuclei stained with DAPI (blue, A and B). Immunohistochemical analysis of control pituitaries revealed the majority of somatotropes express both IGFIR and INSR (merge pictures of A and B [yellow], where * marks the nucleus of a receptor positive somatotrope. In HiGH pituitaries receptor expression is lost, where # marks a GH-immunopositive cell that lacks the receptor signal. However, in HiGH pituitaries, GH-immunonegative cells maintain immunostaining for IGFIR and INSR (@ marks an example of a GH-immunonegative cell that retains receptor signal).

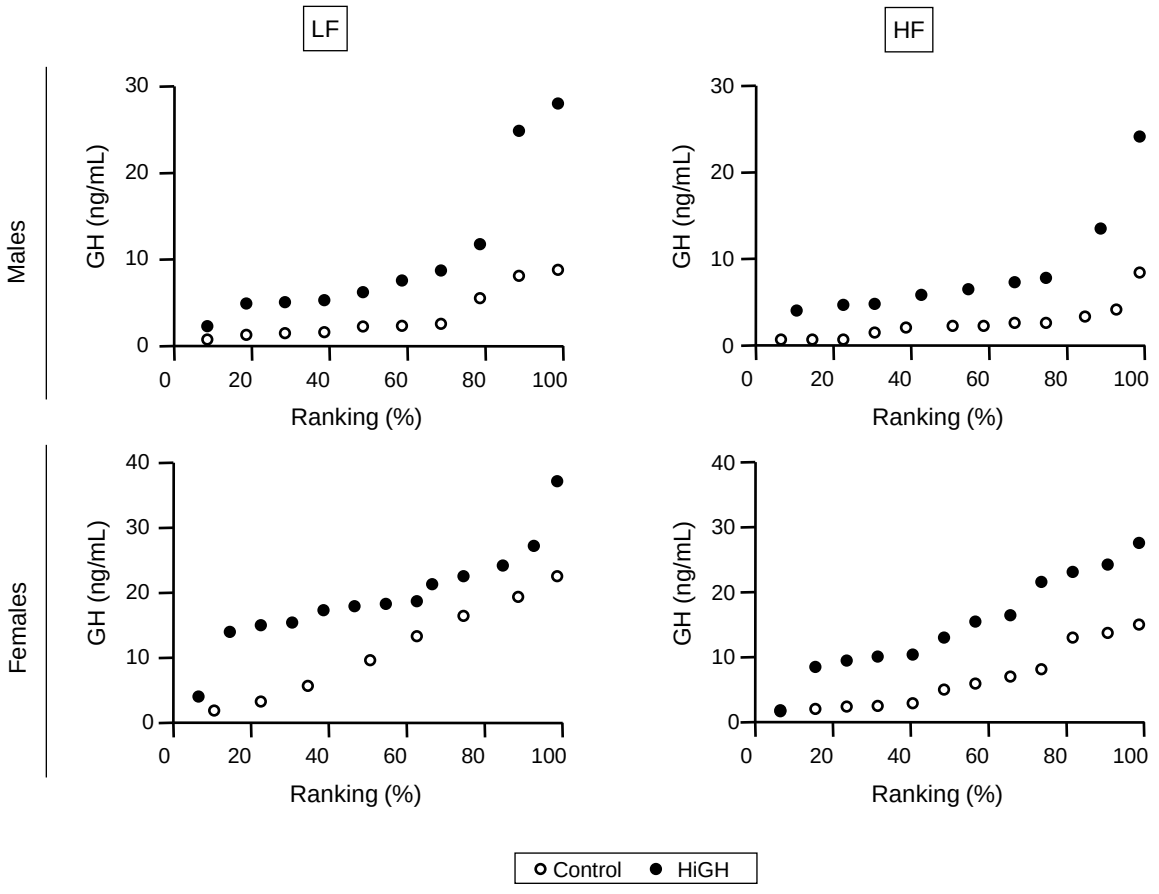

Fig. S2. Rank plot of plasma GH levels in 16 weeks old fasted (18h) male (upper panels) and females (lower panels) LF (left panels) and HF (right panels) IgfIr,Insr^{rGHpCre} (HiGH) and IgfIr,Insr$^{fl/fl}$ (control) mice. Values correspond to fasted samples of n=10-12 mice.

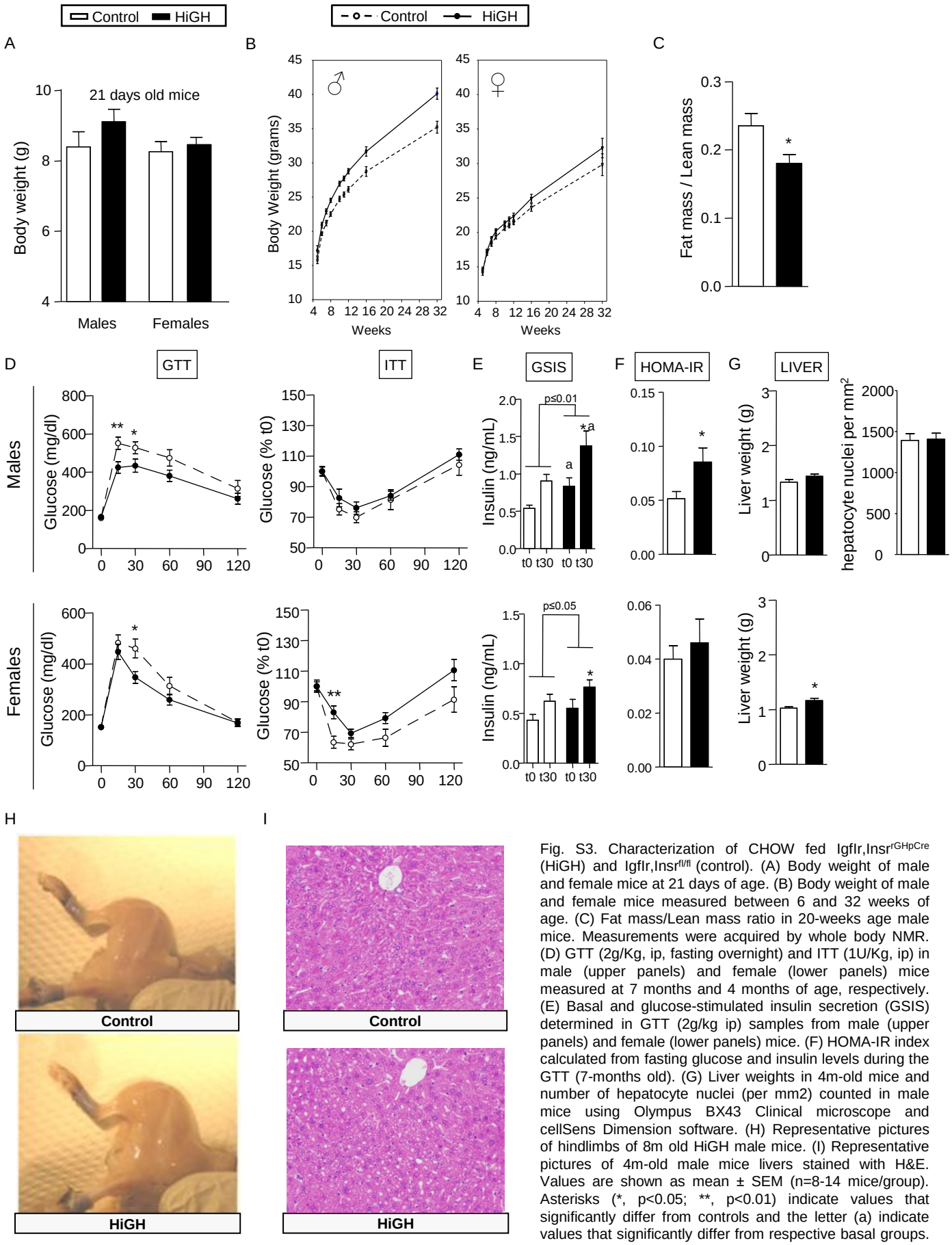

Fig. S3. Characterization of CHOW fed IgfIr,Insr^{rGHpCre} (HiGH) and IgfIr,Insr$^{fl/fl}$ (control). (A) Body weight of male and female mice at 21 days of age. (B) Body weight of male and female mice measured between 6 and 32 weeks of age. (C) Fat mass/Lean mass ratio in 20-weeks age male mice. Measurements were acquired by whole body NMR. (D) GTT (2g/Kg, ip, fasting overnight) and ITT (1U/Kg, ip) in male (upper panels) and female (lower panels) mice measured at 7 months and 4 months of age, respectively. (E) Basal and glucose-stimulated insulin secretion (GSIS) determined in GTT (2g/kg ip) samples from male (upper panels) and female (lower panels) mice. (F) HOMA-IR index calculated from fasting glucose and insulin levels during the GTT (7-months old). (G) Liver weights in 4m-old mice and number of hepatocyte nuclei (per mm2) counted in male mice using Olympus BX43 Clinical microscope and cellSens Dimension software. (H) Representative pictures of hindlimbs of 8m old HiGH male mice. (I) Representative pictures of 4m-old male mice livers stained with H&E. Values are shown as mean ± SEM (n=8-14 mice/group). Asterisks (*, p<0.05; **, p<0.01) indicate values that significantly differ from controls and the letter (a) indicate values that significantly differ from respective basal groups. p-values indicate the effect of the genotype in the observed changes by 2-way ANOVA.

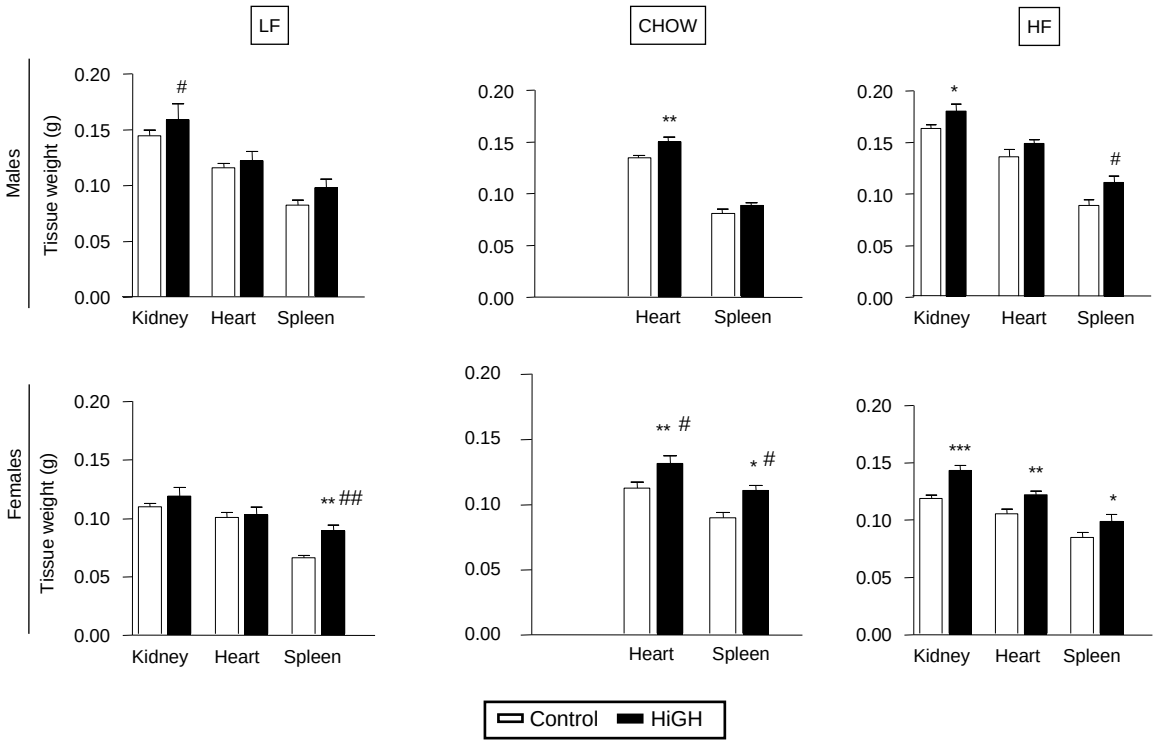

Fig. S4. Kidney, heart, and spleen weights of the IgfIr,Insr^{rGHpCre} (HiGH) and IgfIr,Insr$^{fl/fl}$ (control) at sacrifice. Male (upper panels) and female (lower panels) mice fed a LF (20 weeks of age, left panels), chow (28 weeks of age, middle panels), or HF (20 weeks of age, right panels). Values are shown as mean ± SEM (n=8-14 mice/group). Asterisks (*, p<0.05, **, p<0.01, ***, p<0.001) indicate values that significantly differ from controls. Pound signs ($^{\#}$, p<0.05, $^{\#\#}$, p<0.01) indicate values that significantly differ from controls when adjusted with body weight (BW).

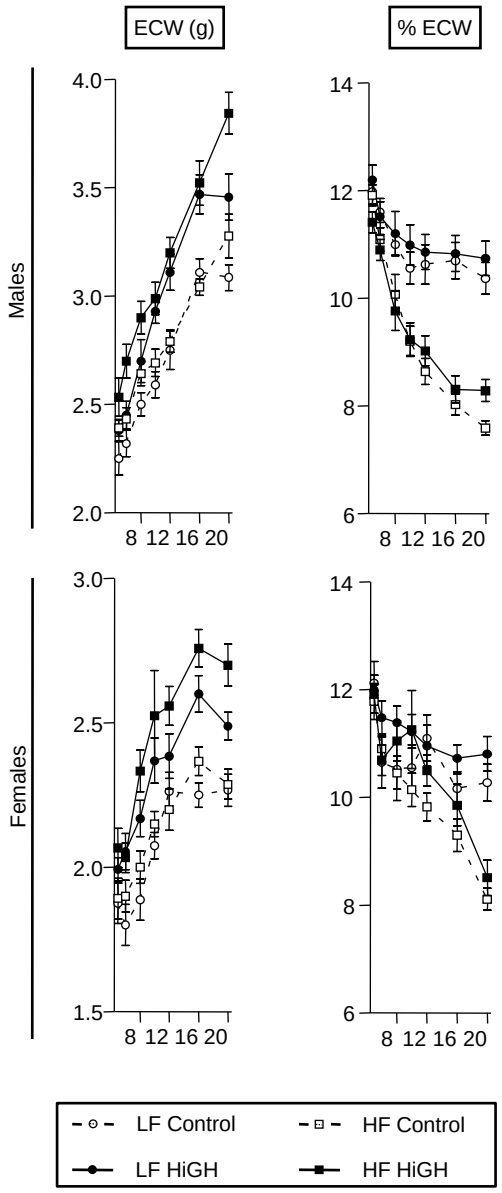

Fig. S5. Extracellular water (ECW, left panels) and % of ECW (right panels) in male (upper panels) and female (lower panels) Igf1r,Insr^{rGHpCre} (HiGH) and Igf1r,Insr$^{fl/fl}$ (control) mice fed a LF or a HF diet. Measurements were acquired by whole body NMR from 5 to 20 weeks of age. Values are shown as mean ± SEM (n=8-14 mice/group).

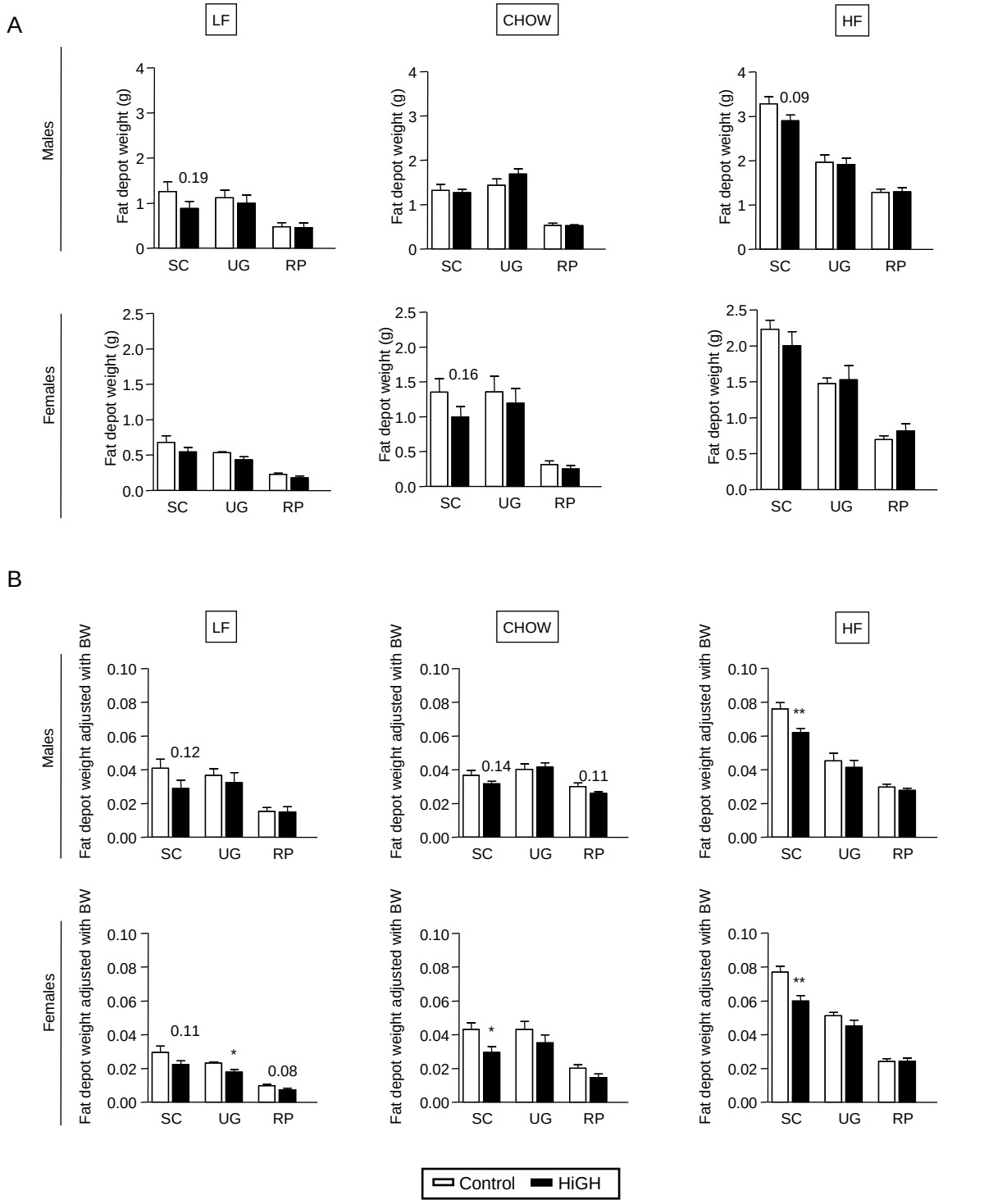

Fig. S6. Absolute fat depots weights (A) and fat depots weights adjusted by body weight (B) in IgfIr,Insr^{rGHpCre} (HiGH) and IgfIr,Insr$^{fl/fl}$ (control) mice at sacrifice. Male (upper panels) and female (lower panels) mice fed a LF (20 weeks of age, left panels), chow (28 weeks of age, middle panels), or HF (20 weeks of age, right panels). SC, subcutaneous; RP, retroperitoneal; UG, urogenital. Values are shown as mean ± SEM (n=8-14 mice/group). Asterisks (*, p<0.05, **, p<0.01) indicate values that significantly differ from controls.

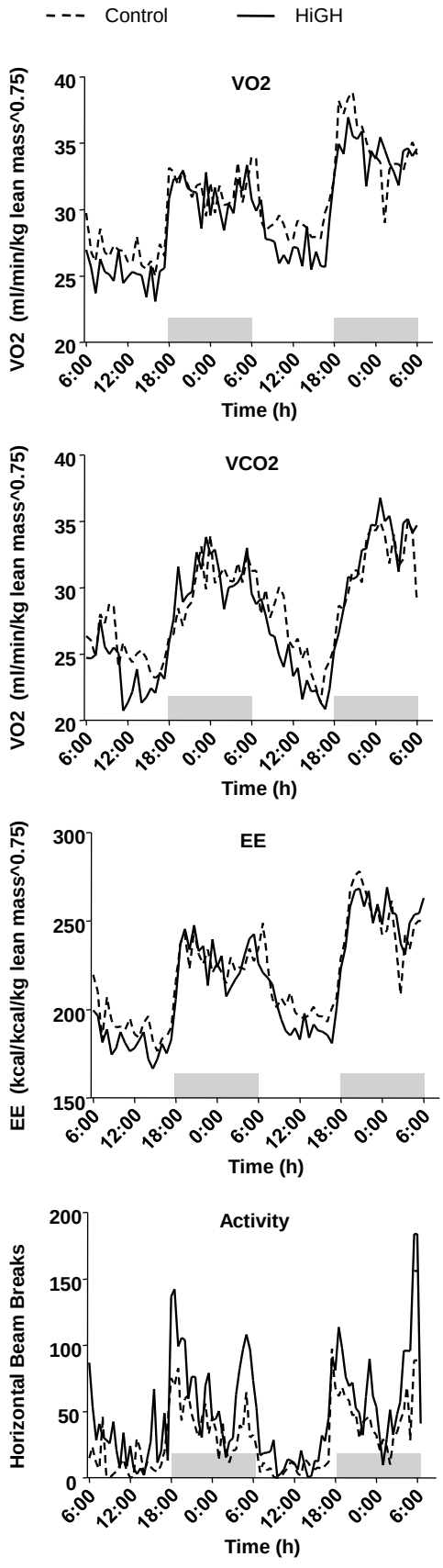

Fig. S7. Mean 48h profiles of VO2, VCO2 and energy expenditure (EE, kcal/day/kg$^{0.75}$) of LF-fed IgfIr,Insr^{rGHpCre} (HiGH) and IgfIr,Insr$^{fl/fl}$ (control). Data was pooled from two separate runs using different 10-week old mice in each run (n=10 mice/group).