Fig.S1

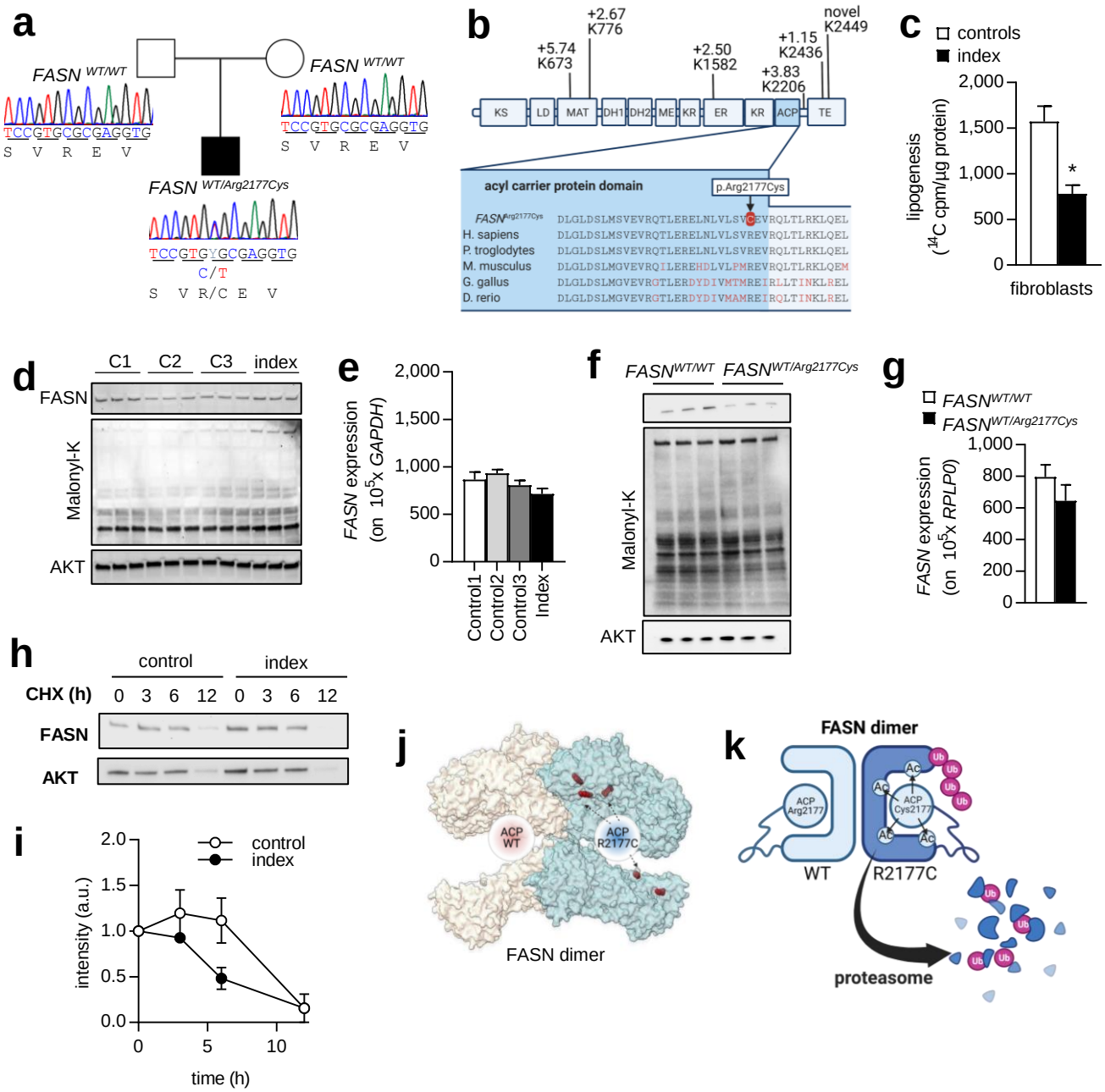

Fig.S1: Functional analysis of a FASN^{Arg2177Cys} variant. (a) Pedigree tree of the affected family indicating a heterozygous de novo variant in FASN [c.6529C>T (p.Arg2177Cys)] and wild type (WT) FASN loci of the parents found by trio-whole exome sequencing with sequencing traces of confirmative sanger sequencing of parents and index patient indicating a de novo missense mutation in FASN. (b) Localization of missense variant in the ACP domain and conservation of the amino acid. K indicates mass spec-defined acetyl-lysine sites and fold induction of the positively altered acetylation sites is indicated. (c) ^{14}C-acetate incorporation into triacylglycerols in patient fibroblasts and controls. (d) Western blot of control and index fibroblasts indicating malonyl-lysine posttranslational modifications, a surrogate marker for intracellular malonyl-CoA (e) *FASN* gene expression in fibroblasts and controls. (f) Western blot and (g) gene expression of FASN$^{WT/WT}$ and FASN$^{WT/Arg2177Cys}$-HepG2 cells. (h) Western blot and (i) quantification of western blots (n=2 independent experiments) indicating reduced FASN stability in index fibroblasts (j) Computational structural model of a putative WT and FASN^{Arg2177Cys} dimer. Hyperacetylated lysines are marked in red. (k) Proposed model of the protein instability. FASN^{Arg2177Cys} is non-enzymatically acetylated by the missense cysteine, which is recognized and ubiquitinylated by E3-ligases and further degraded by the proteasome.

Fig.S2

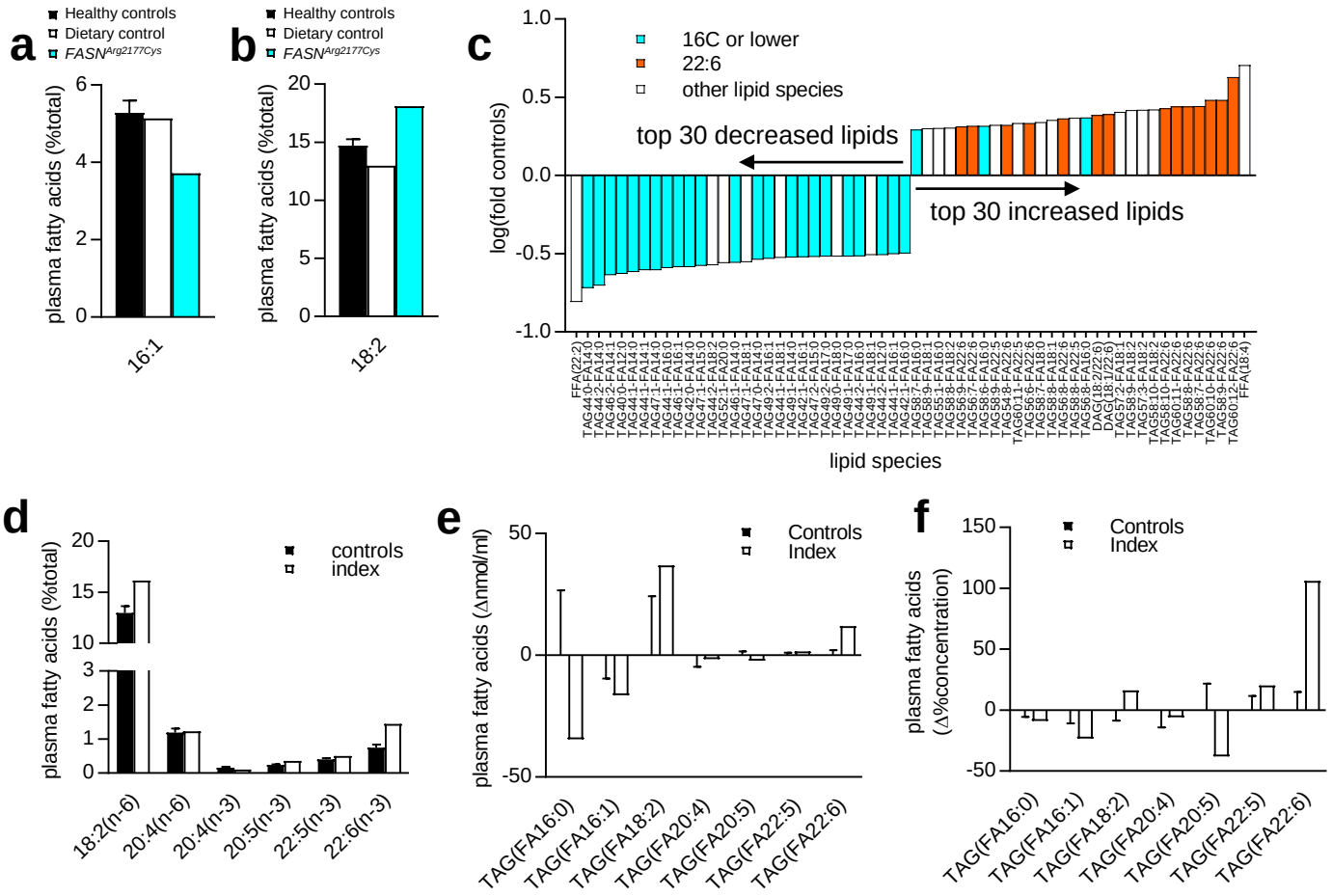

Fig.S2: Lipidomics of genetic FASN modulation. Panel (a + b) show the values, which have been used to calculate the lipogenic index in main Fig.2a. (c) Plot of top 30 increased/decreased log-transformed fold induction of all investigated lipid classes compared to the mean of healthy control patients. “16C or lower” indicates all lipid species with fatty acid residues of 16 carbon atoms or lower (independent of desaturation) and 22:6 indicates existing docosahexaenoic acid residues within the investigated lipid. Plot (d) shows percentage of the indicated PUFAs linoleic acid [18:2(n-6)], arachidonic acid [20:4(n-6)], eicosapentaeic acid [20:4(n-3)], eicosapentaenic acid [20:5(n-3)], docosapentaenic acid [22:5(n-3)] and docosahexaenoic acid [22:6(n-3)] in TAG. (e) shows the delta of absolute concentrations and (f) the delta of the percentage of the indicated fatty acid species in the TAG lipid class in the index patient compared to TAG-matched controls. Error bars are indicating standard error of the mean (SEM).

Fig.S3

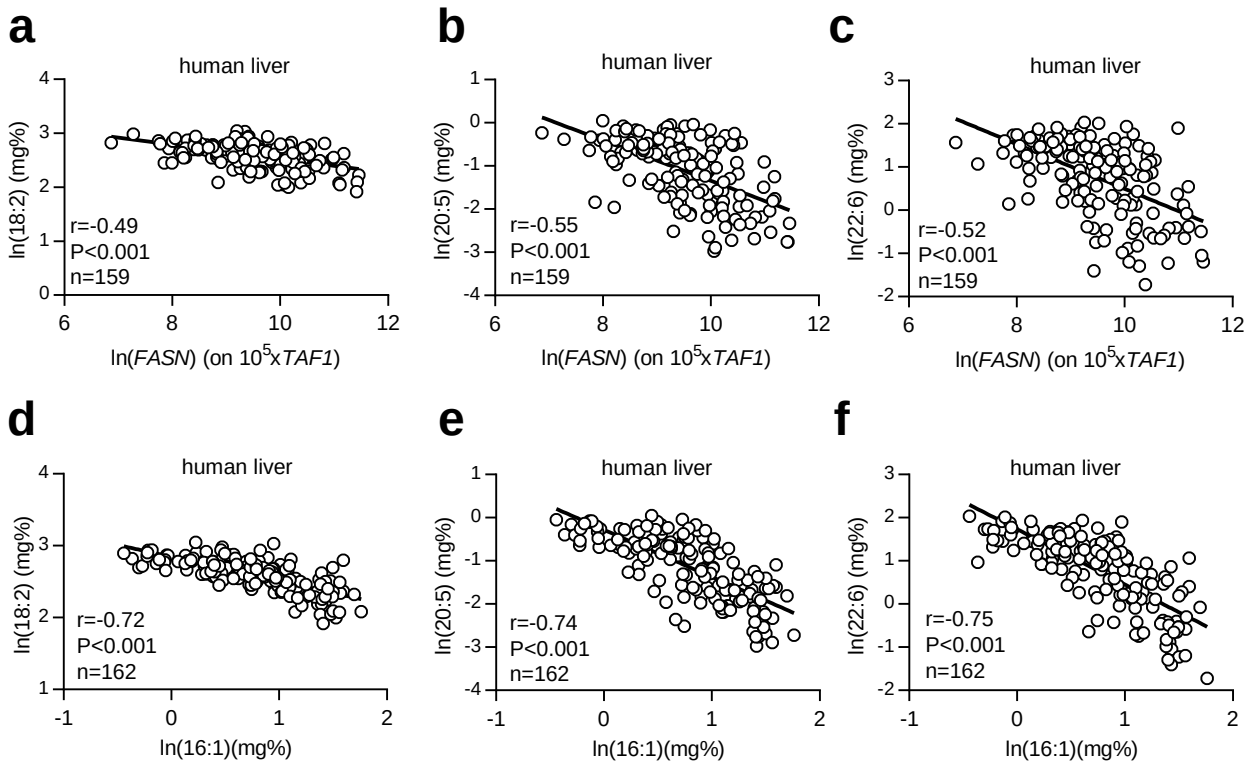

Fig.S3: Fatty acids in TAG of obesity-associated FASN modulation. Correlation of liver fatty acid measurements of log-transformed linoleic acid (18:2), eicosapentaenoic acid (20:5) and docosahexaenoic acid (22:6) to *FASN* gene expression (a-c) or palmitoleate concentration (c-e). Pearson correlation coefficient (r) was used to estimate correlation of linear regression analysis. Statistical significance was assumed at a level of P<0.001 for linear regression analysis.

Fig.S4

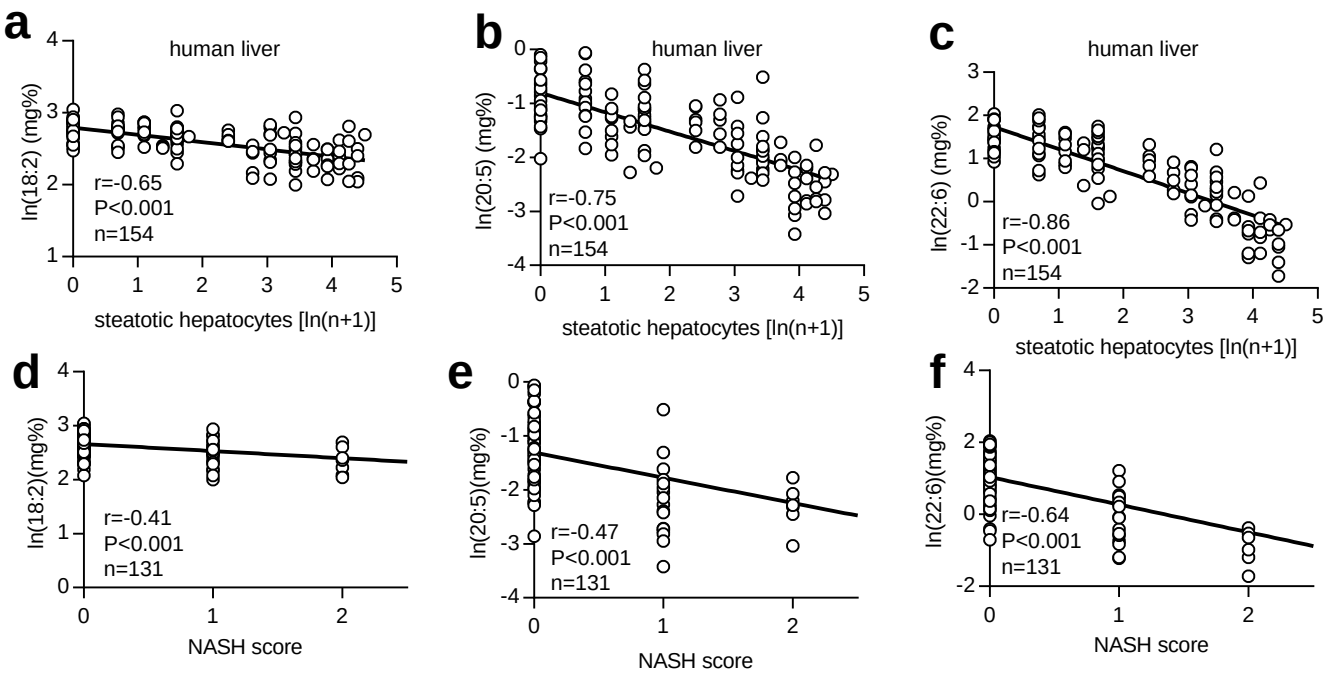

Fig.S4: Liver pathology score correlations to the FASN expression. Correlations of log-transformed linoleic acid (18:2), eicosapentaenoic acid (20:5) or docosahexaenoic acid (22:6) to histologically confirmed steatotic hepatocytes (a-c) respectively NASH-Score (d-f). Pearson correlation coefficient (r) was used to estimate correlation of linear regression analysis and statistical significance was assumed at a level of P<0.001.

Fig.S5

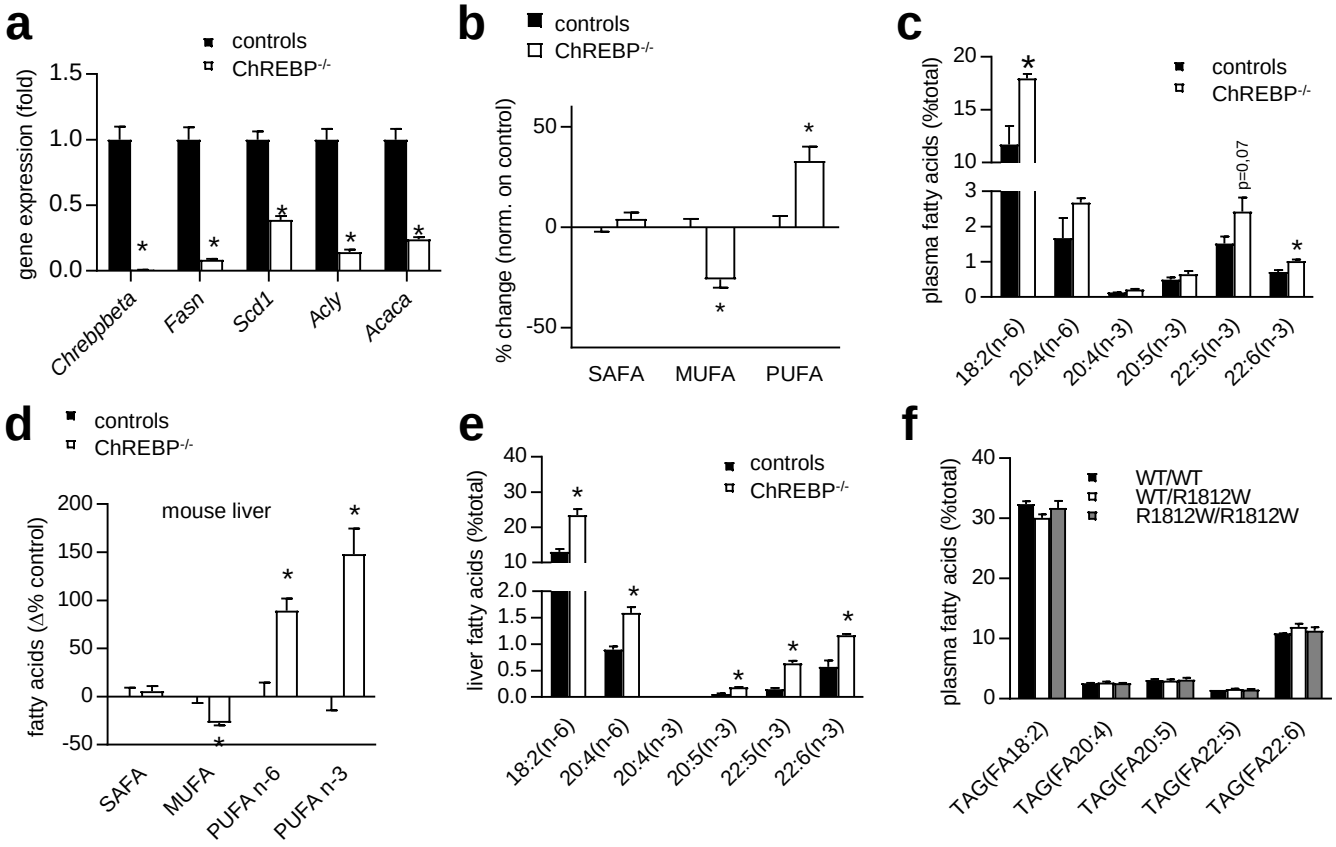

Fig.S5: *ChREBP*$_{-/-}$ mice, a mouse model of low lipogenesis, phenocopy the higher PUFA abundance. (a) Gene expression of liver of wild type or *ChREBP*$^{-/-}$ mice. (b) LC-MS plasma fatty acid composition. (c) GC-FiD analysis of different n-6 and n-3 PUFA species in TAG fraction of thin layer chromatography of wild type and *ChREBP*$^{-/-}$ mice. (d-e) Liver fatty acid composition of different n-6 and n-3 PUFA species in triacylglycerol fraction of thin layer chromatography of wild type and *ChREBP*$^{-/-}$ mice. (f) LC-MS plasma fatty acid composition analysis of TAG of wild type, heterozygous or homozygous FASN-R1812W transgenic mice. * indicates $p<0.05$ by calculation of students T-Test. Error bars are indicating standard error of the mean (SEM).

Fig.S6

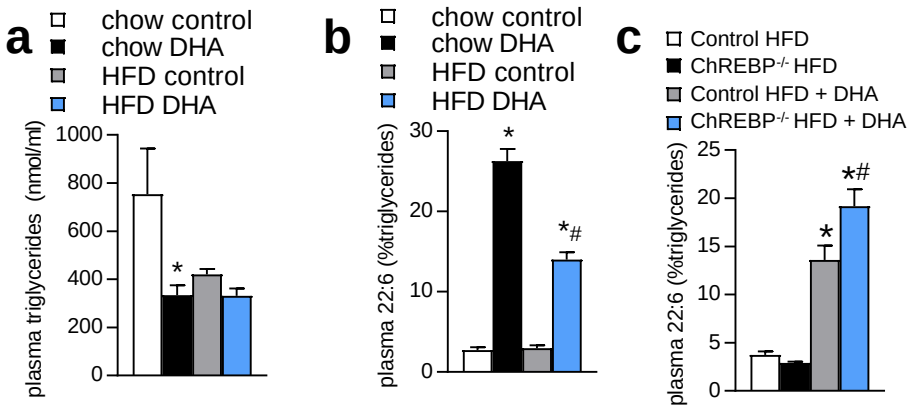

Fig.S6: DHA supplementation in genetically low lipogenesis ChREBP$^{-/-}$ mice. (a) plasma TAG and (b) plasma docosahexaenoic acid (22:6) of mice fed a chow diet with or without supplementation of docosahexaenoic (DHA). (c) Plasma triglycerides of wild type or ChREBP-/- (KO) mice fed a high fat diet supplemented with or without docosahexaenoic acid (DHA). * indicates p<0,05 by calculation of two-way ANOVA vs control respectively # vs supplementation intervention group. Error bars are indicating standard error of the mean (SEM).

Fig.S7

a

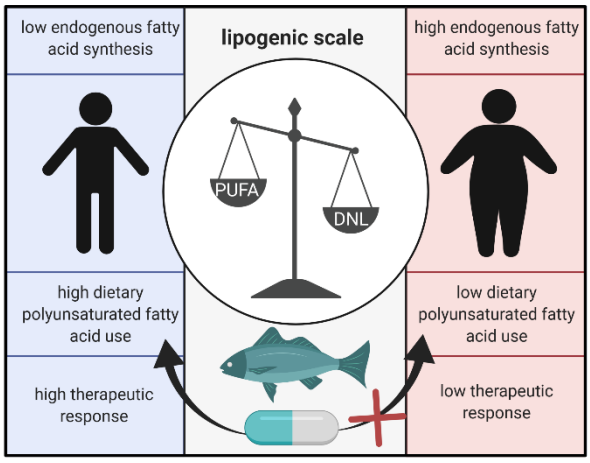

Fig.S7: Working model. (a) Model of PUFA use in lean respectively obese patients. Endogenous fatty acids derived from de novo lipogenesis (DNL) suppress the incorporation of exogenous PUFA and might lead to reduced therapeutic responses.