

Supplemental information

**Genetic background and sex
control the outcome of high-fat
diet feeding in mice**

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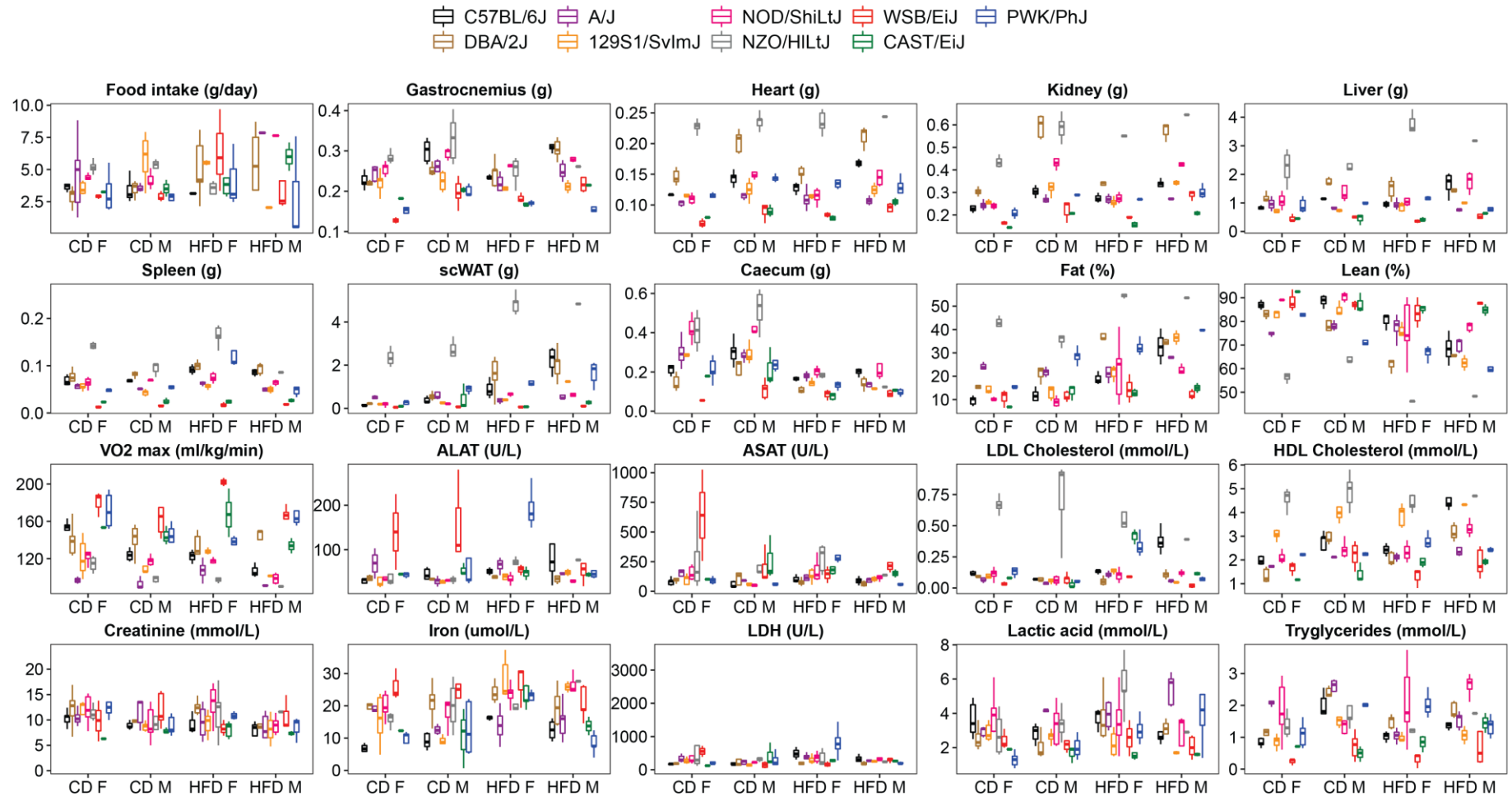


Figure S1, Related to Figures 1 and 2: Selected metabolic traits measured in this study: Boxplots of the food intake, organ weights, Echo-MRI, VO₂ max and plasma biochemistry data across all strains and conditions. Due to the large number of conditions, comparisons were pictured in the heatmap figure 1C. Daily food intake in individual mice was measured automatically in the metabolic cages (CLAMS). 23 mice on HFD “played with the food” i.e. dispersed large amounts of food pellets into the cage, and had to be excluded from quantification, greatly reducing the number of replicates for food intake in HFD-fed animals.

The naturally obese and glucose intolerant NZO/HILtJ strain emerges as an outlier in organ weights and fat mass, as well as plasma cholesterol measurements. This data can be explored in further detail through our online interface at https://lisp-lms.shinyapps.io/Project_CC_Founder_App/.

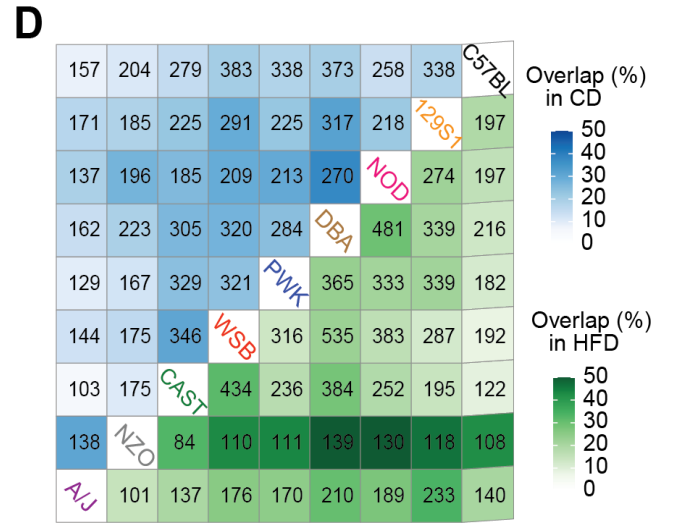
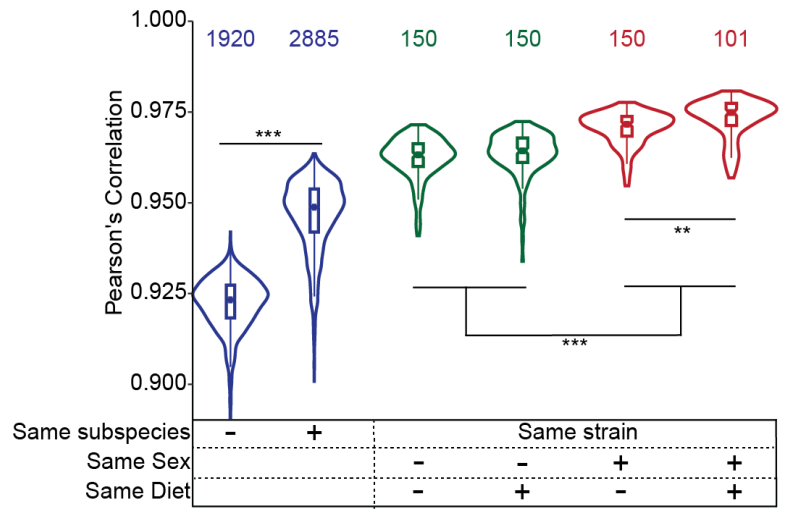
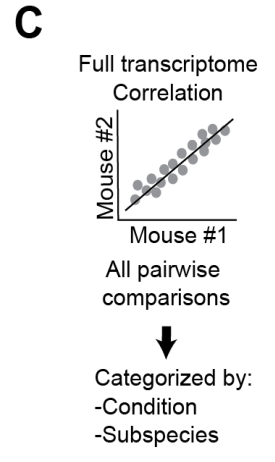
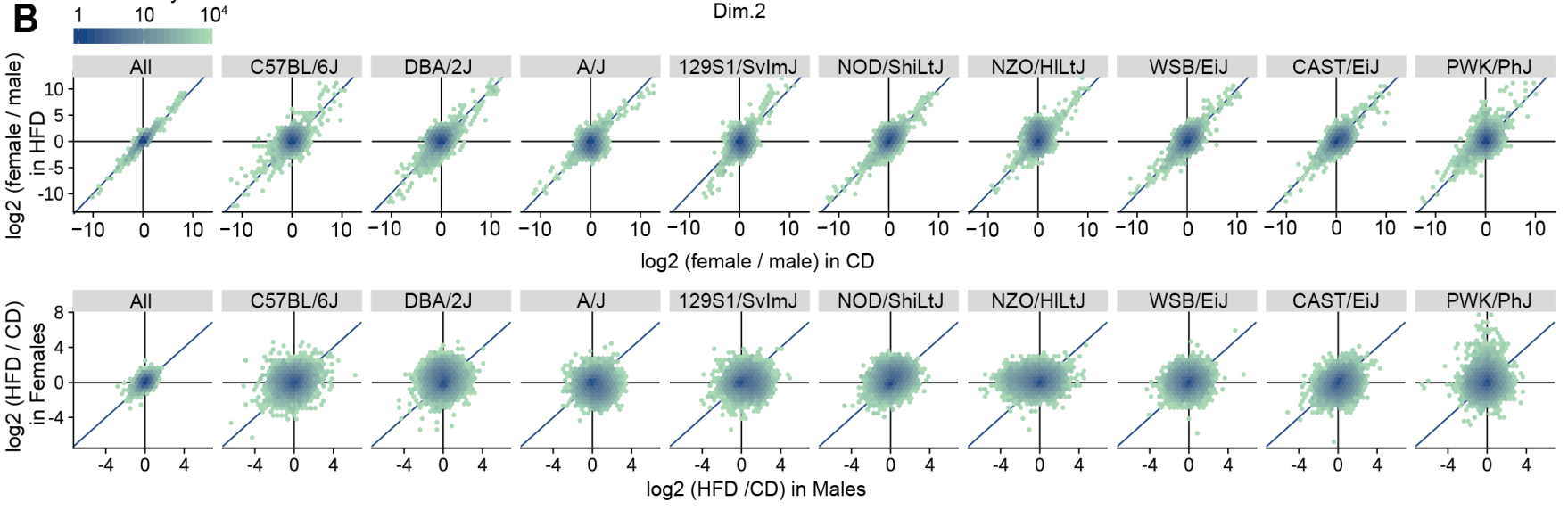
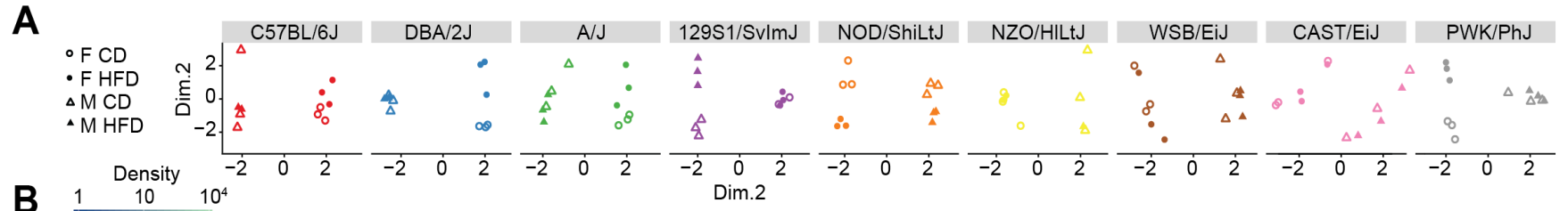


Figure S2, Related to Figure 4: Strain-specific liver gene expression response to diet of is not well conserved across sexes.

A) Multidimensional scaling (MDS) for transcriptomic data. Euclidean distances between each strain were calculated pairwise based on the leading \log_2 -fold changes for the 500 most differentially expressed genes. Each dot represents a mouse in a given condition, which is in turn associated with a specific shape. The effect of sex is predominant compared to the effect of the diet, which can be seen in some strains for one or both sexes.

B Top: overall and per-strain correlation plots of sex effects (\log_2 fold changes of female vs male) in CD vs HFD. Bottom: overall and per-strain correlation plots of diet effects (\log_2 fold changes of HFD vs CD) in females vs. males. Sex differences are well conserved between CD and HFD as well as between strains. Diet differences are qualitatively and quantitatively poorly conserved across sexes and strains. Sex differences are well conserved between CD and HFD as well as between strains. Diet differences are qualitatively and quantitatively poorly conserved across sexes and strains.

C) Pearson's correlation of pairwise mice comparisons of global gene expression. Note a strong effect of subspecies differences on transcriptomic profiles. The effects of sex and diet are subordinate to the subspecies effect.

D) Number (written) and percentage (color legend) of overlapping genes that are differentially expressed between females and males, in CD (blue) or HFD (green).