

Effects of APOE4 and TREM2 R47H mutations on the gut microbiome in the hAbKI Alzheimer's mouse model



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INTRODUCTION

- The hAbKI mouse carries humanized A β sequences. Stacking APOE4 and TREM2 R47H onto this background enables controlled dissection of additive AD risk gene effects in vivo.
- Sex hormones and the gut microbiome are engaged in bidirectional crosstalk, and emerging evidence links this interaction to sex-specific patterns of neurodegeneration through the gut-brain axis [1].
- Here, using MetaPhlAn4 on MODEL-AD mice of 4 genotypes $\times$ 4 ages, we show that APOE4 and TREM2 R47H selectively alter the female cecal microbiome at mid-life, mirroring APOE4's disproportionate AD risk in women [2].

KEY TAKEAWAYS

- A.** Housing dominates microbiome variance across all genotypes, followed by sex and genotype. Sex-driven variance peaks at 12 months.
- B.** Sex-associated microbiome variance is genotype-dependent: each additional AD mutation amplifies the sex effect at 12 months, a pattern that emerges later (18 months) in WT mice.
- C.** APOE4 and APOE4+TREM2 drive the greatest number of DA taxa in females at 12 months, indicating mid-life as a critical window for genotype-driven microbiome disruption.

CONCLUSIONS

Sex-associated microbiome variance is genotype-dependent, amplifying progressively with each AD mutation and peaking at 12 months. 12 months is an age coinciding with the onset of reproductive aging in female mice and the perimenopausal transition in women (aged 40-50 years) [3]. APOE4 and APOE4+TREM2 R47H selectively alter the female cecal microbiome at mid-life, consistent with the estrogen-gut microbiota-brain axis linking perimenopausal estrogen decline to AD-related dysbiosis [4]. As the gut microbiome is modifiable through diet, these findings highlight mid-life as a potential window for sex-specific microbiome-targeted interventions in female AD risk.

RESULTS

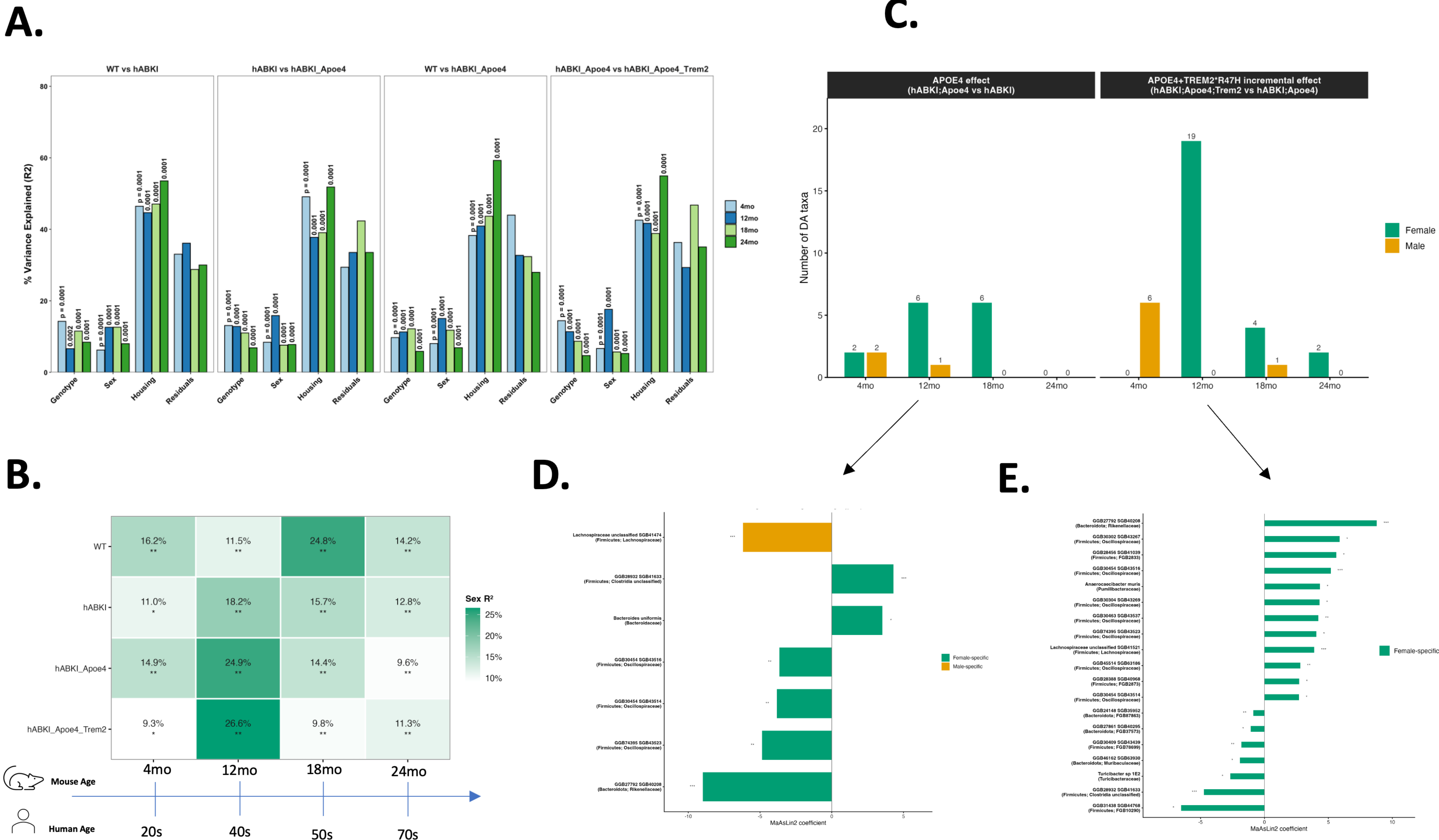


Figure 1. Sex is a dominant, genotype-dependent biological factor shaping the cecal microbiome, and AD risk alleles drive female-specific differential abundance at mid-life. (A) PERMANOVA analysis of four pairwise genotype comparisons across ages (R^2). (B) Heatmap of the variance explained by sex (R^2) within each genotype $\times$ age group. Values represent PERMANOVA R^2 for sex as the predictor (* $p < 0.05$, ** $p < 0.01$). Approximate human age equivalents are indicated below mouse ages. (C) Number of differentially abundant (DA) taxa (MaAsLin2, $q < 0.05$) identified for the APOE4 effect and the APOE4+TREM2 R47H incremental effect, stratified by sex and age. (D-E) Diverging bar charts of MaAsLin2 coefficients for significantly DA taxa at 12 months for the APOE4 effect (D) and the APOE4+TREM2 R47H incremental effect (E). Arrows indicate the 12-month timepoint DA taxa from C.

METHODS

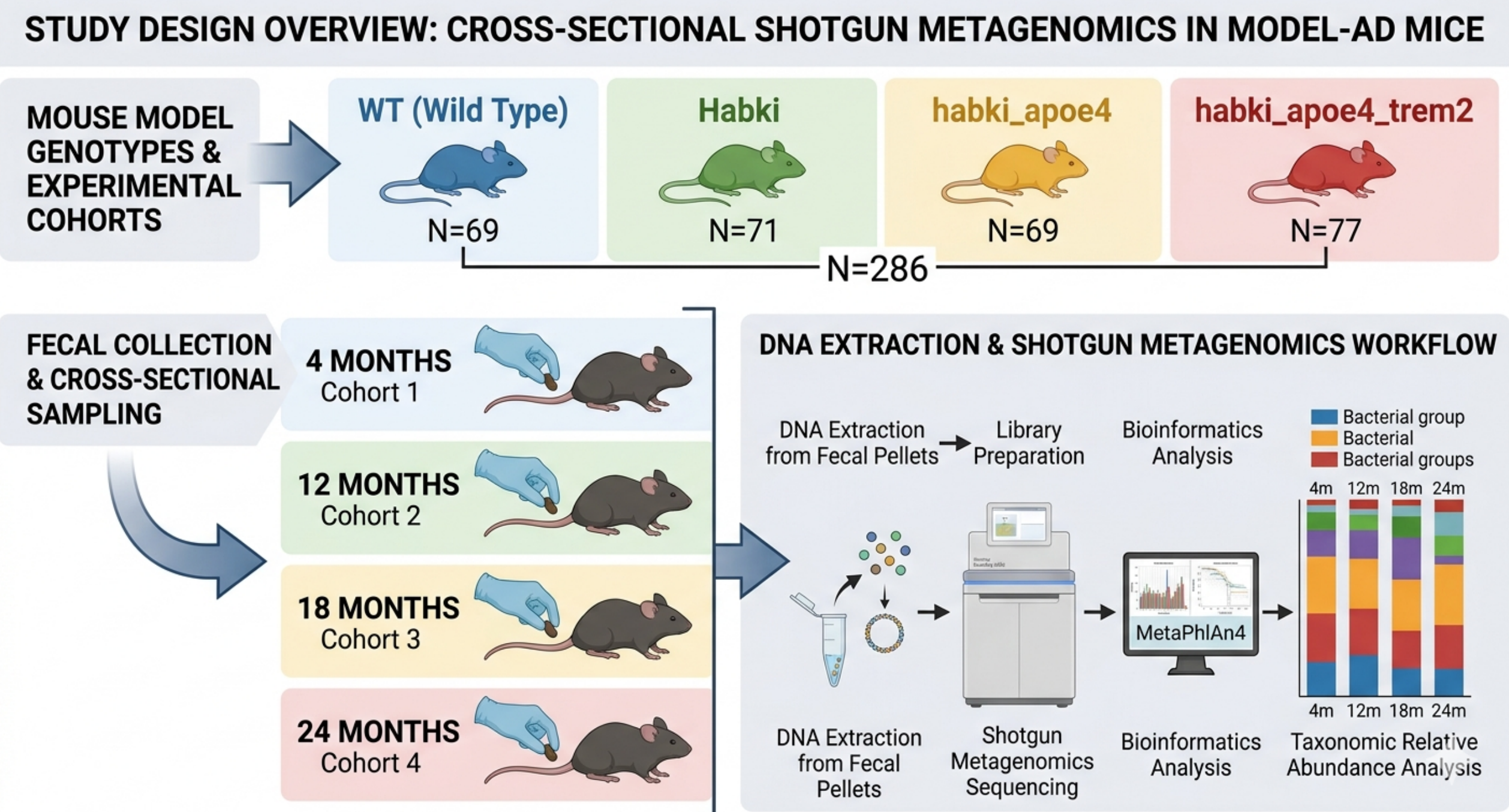


Figure 2. Schematic Overview of methodology

- Cecal microbiome sequences of 4 genotypes $\times$ 4 ages were processed using MetaPhlAn4, for detection of novel unclassified microbial lineages alongside known taxa.
- Community structure was assessed by PERMANOVA; sex-stratified differential abundance was tested using MaAsLin2 with cage as a random effect.

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