



Time-Restricted Feeding Functionally Modulates the Gut Microbiome in a Mouse Model of Non-Alcoholic Steatohepatitis



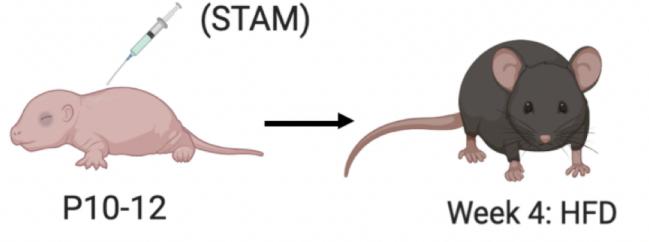
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BACKGROUND

- Non-alcoholic fatty liver disease (NAFLD) affects approximately 30-40% of adults in the US^{1,2}.
- NAFLD can advance to progressive stages, such as nonalcoholic steatohepatitis (NASH), which increases the risk of hepatology-related morbidity and mortality³.
- Disruptions in circadian rhythms and gut microbiome composition are key features of NASH⁴. However, there is currently a gap in knowledge of how these seemingly disparate mechanisms are related to each other or to disease pathogenesis.
- There is a critical need to understand the role of circadian dyssynchrony in the etiology of NAFLD and NASH, and the role that the gut microbiome plays in stabilizing healthful synchrony, or exacerbating damaging dyssynchrony.

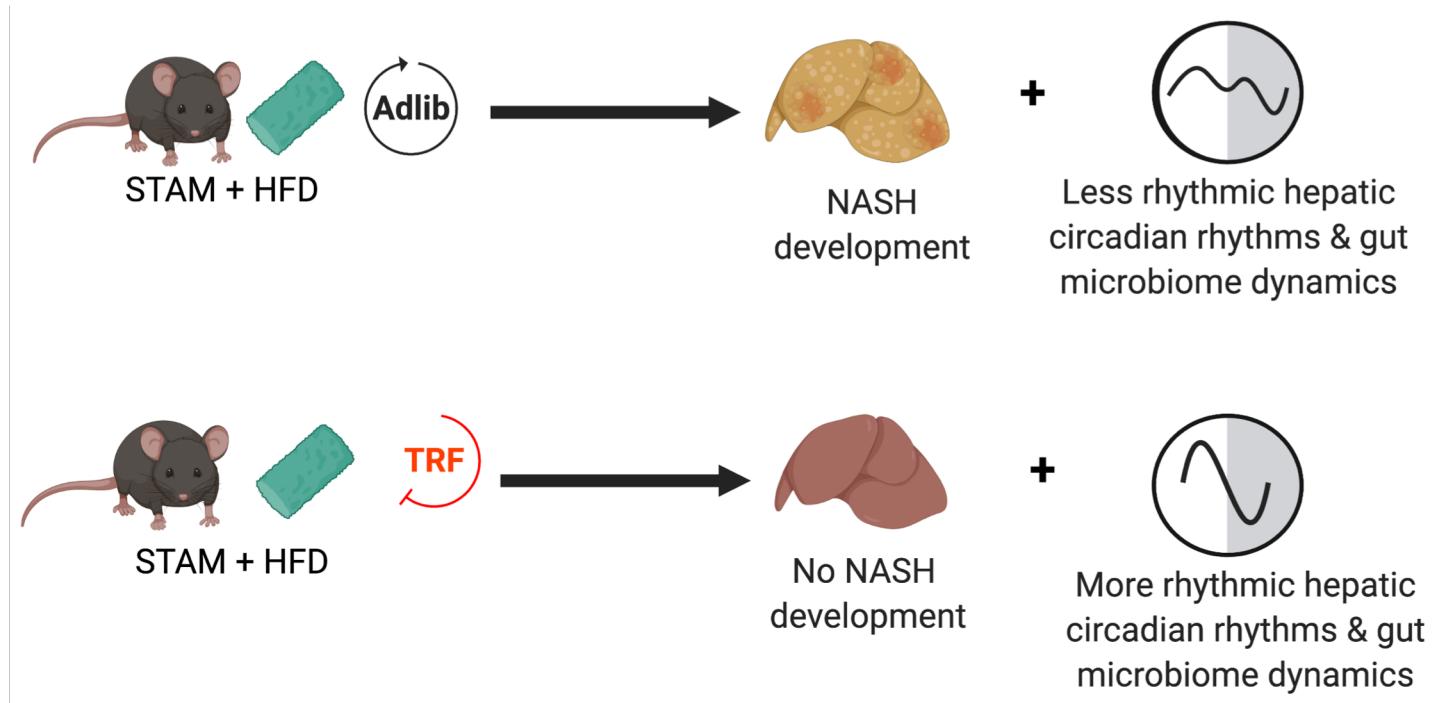
MOUSE MODEL OF NASH: STREPTOZOTOCIN + HFD



- Streptozotocin (**STAM**): kills insulin-producing pancreatic beta cells⁵.
- When combined with high-fat diet (**HFD**), male mice develop NASH by ~12 weeks⁵.
- This model exhibits relevant pathological development under a diabetic background.

HYPOTHESIS

NASH is associated with altered gut microbiome dynamics & disrupted hepatic circadian rhythms, which can be manipulated with feeding pattern to ameliorate disease.



EXPERIMENTAL DESIGN

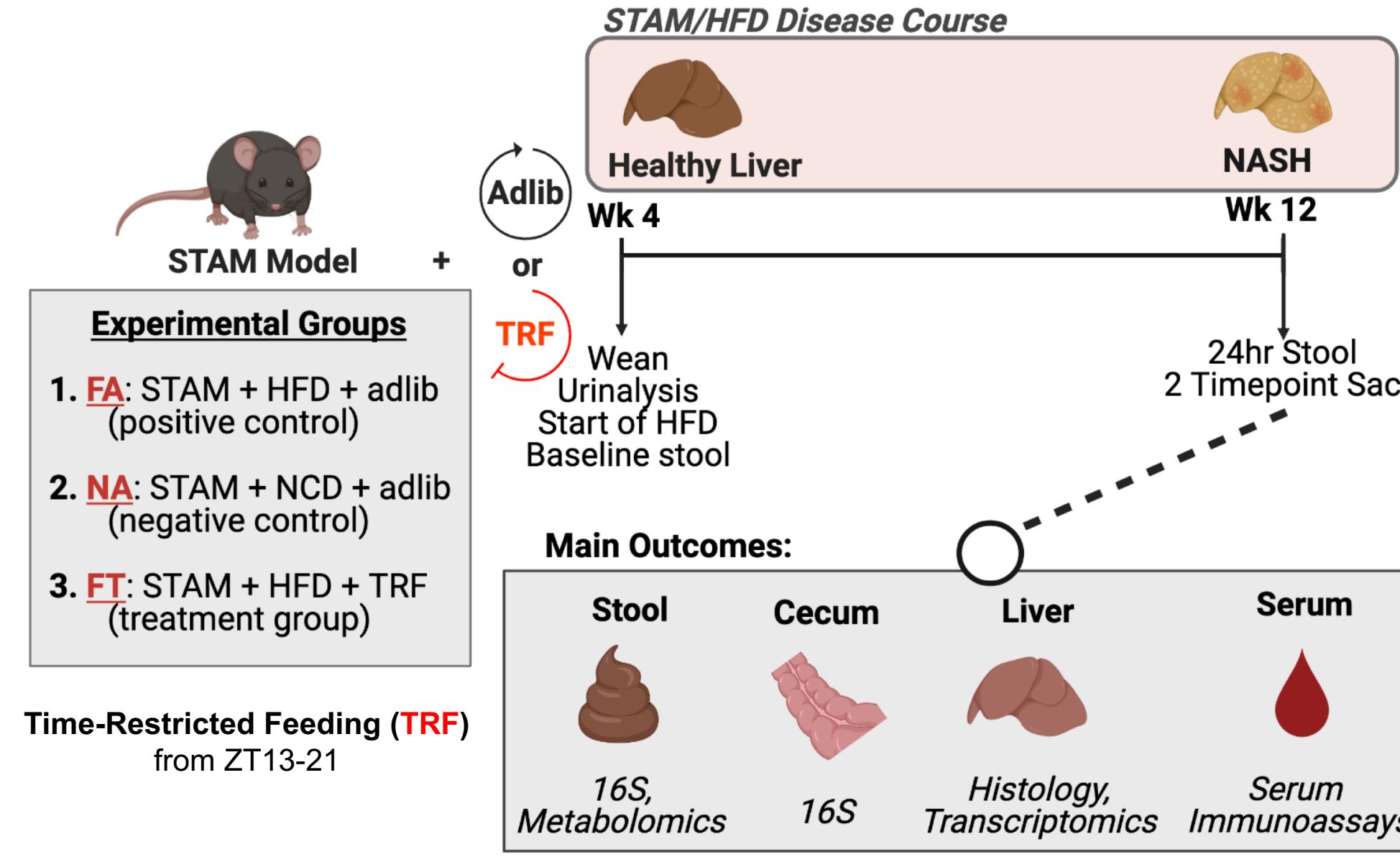


Figure 1: Body weight, food consumption, serum glucose and insulin concentrations of STAM mice on TRF

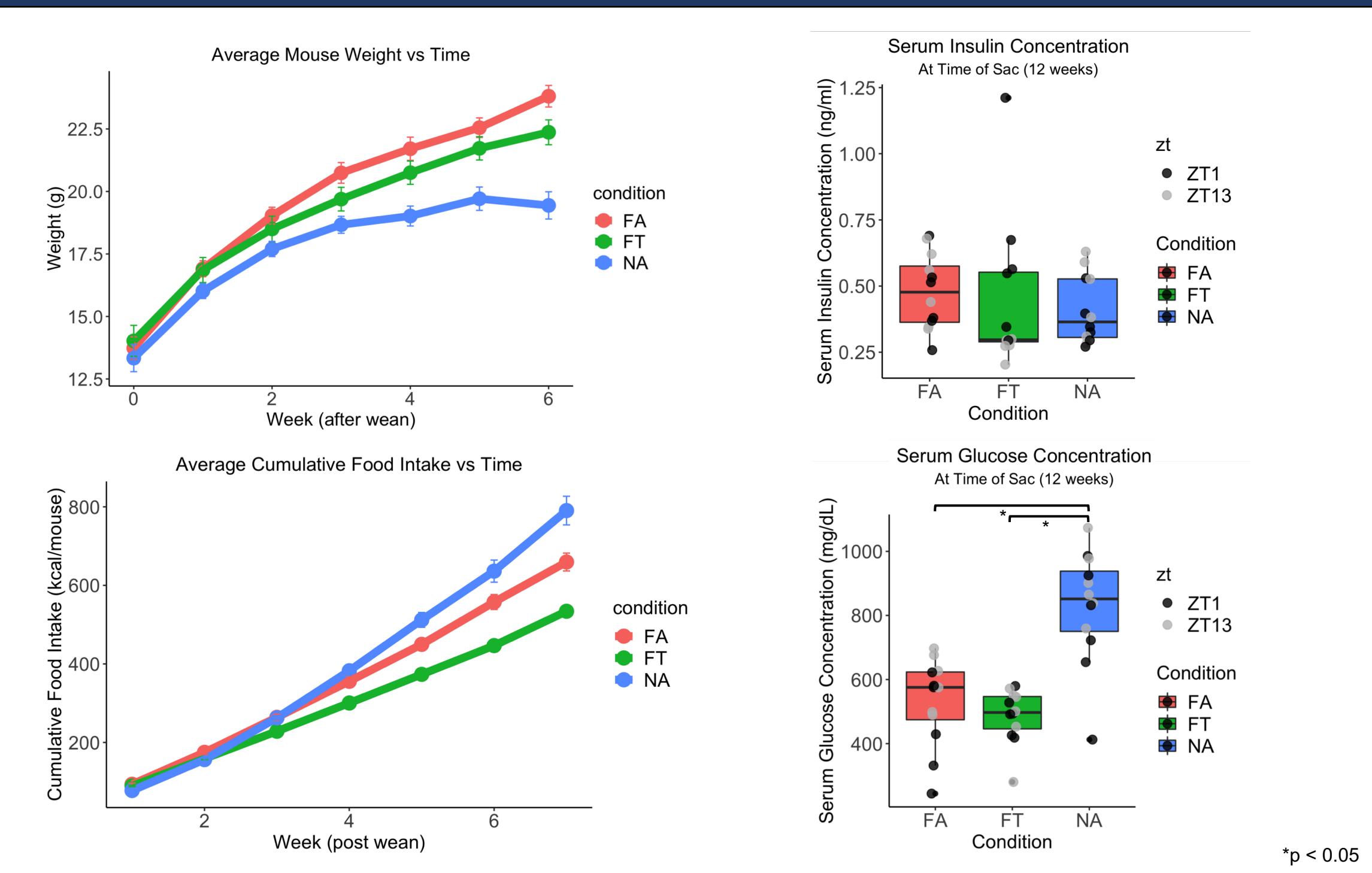


Figure 2: STAM mice on TRF have dynamic changes in cecum microbiome composition

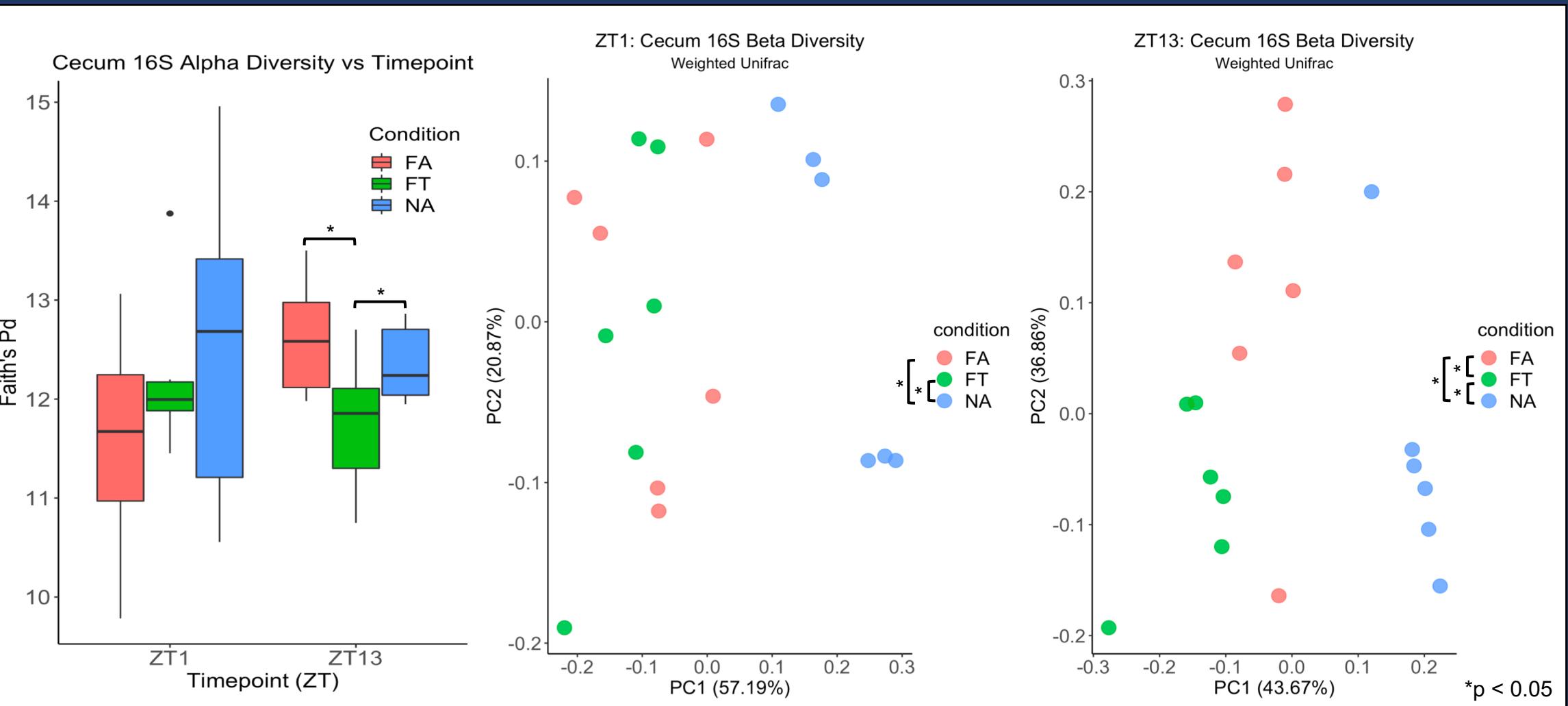


Figure 3: Top features driving compositional differences between STAM FT vs FA mice

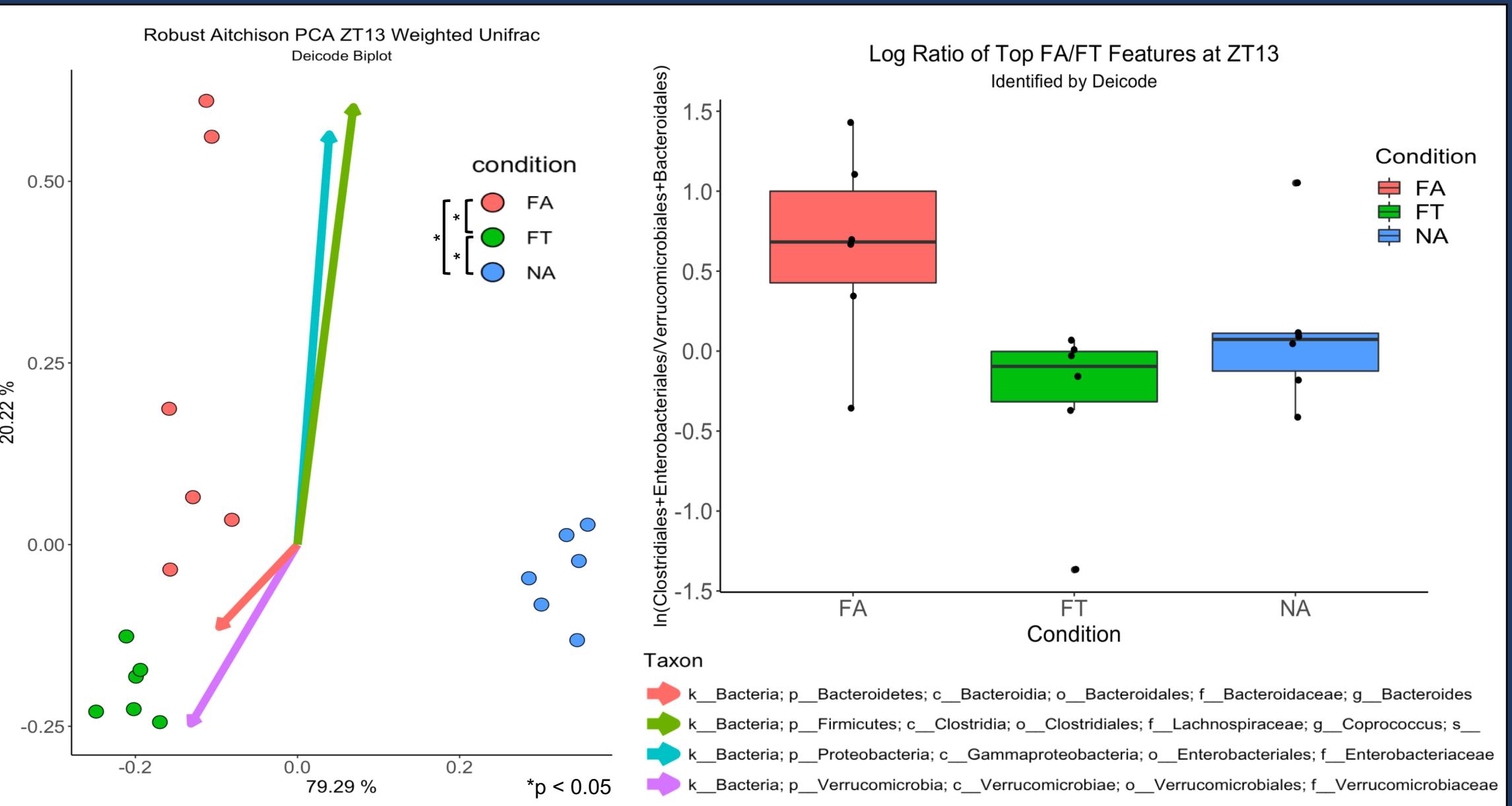


Figure 3: TRF increases bacterially-modified bile acids in stool of STAM Mice

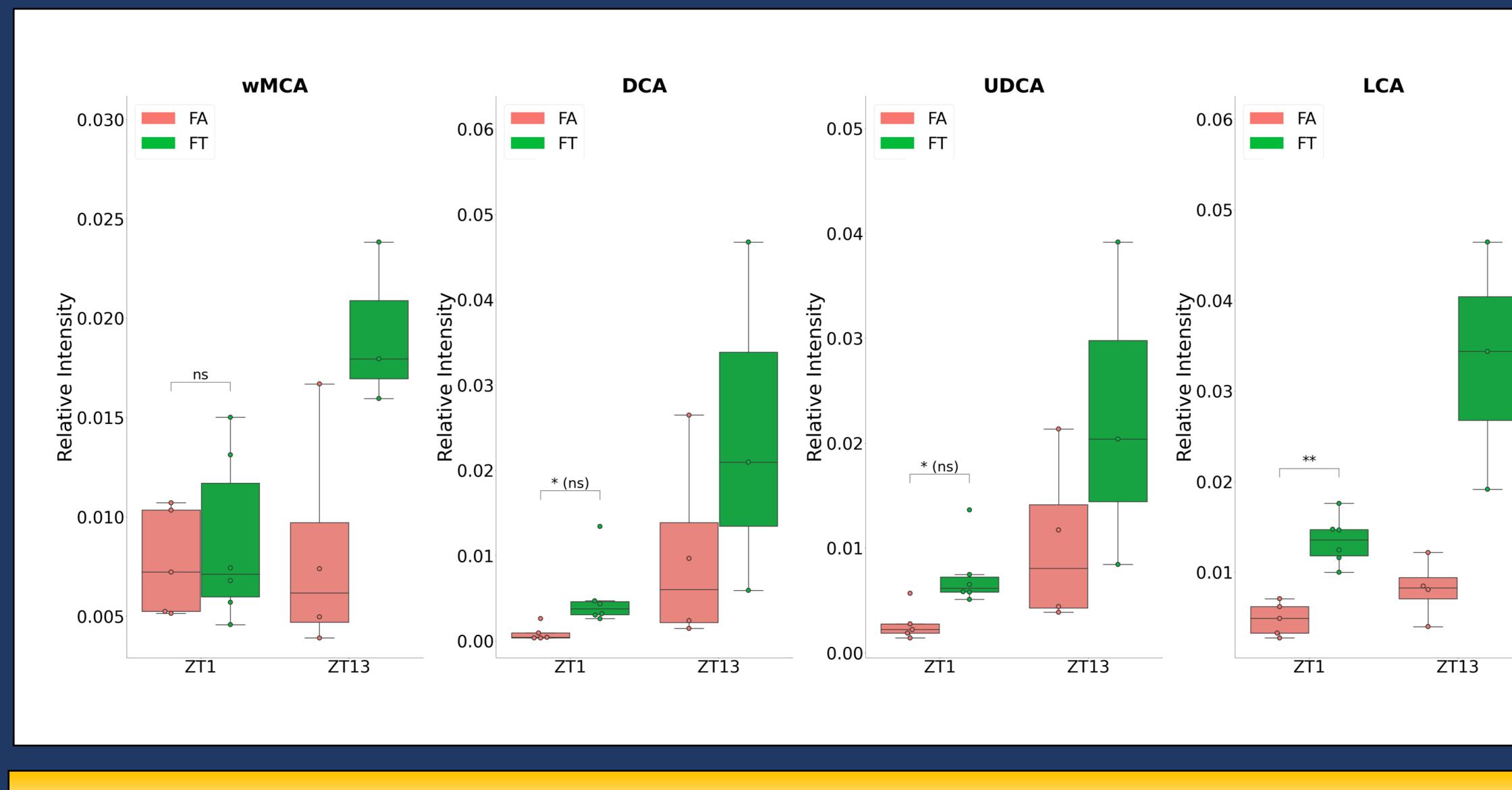
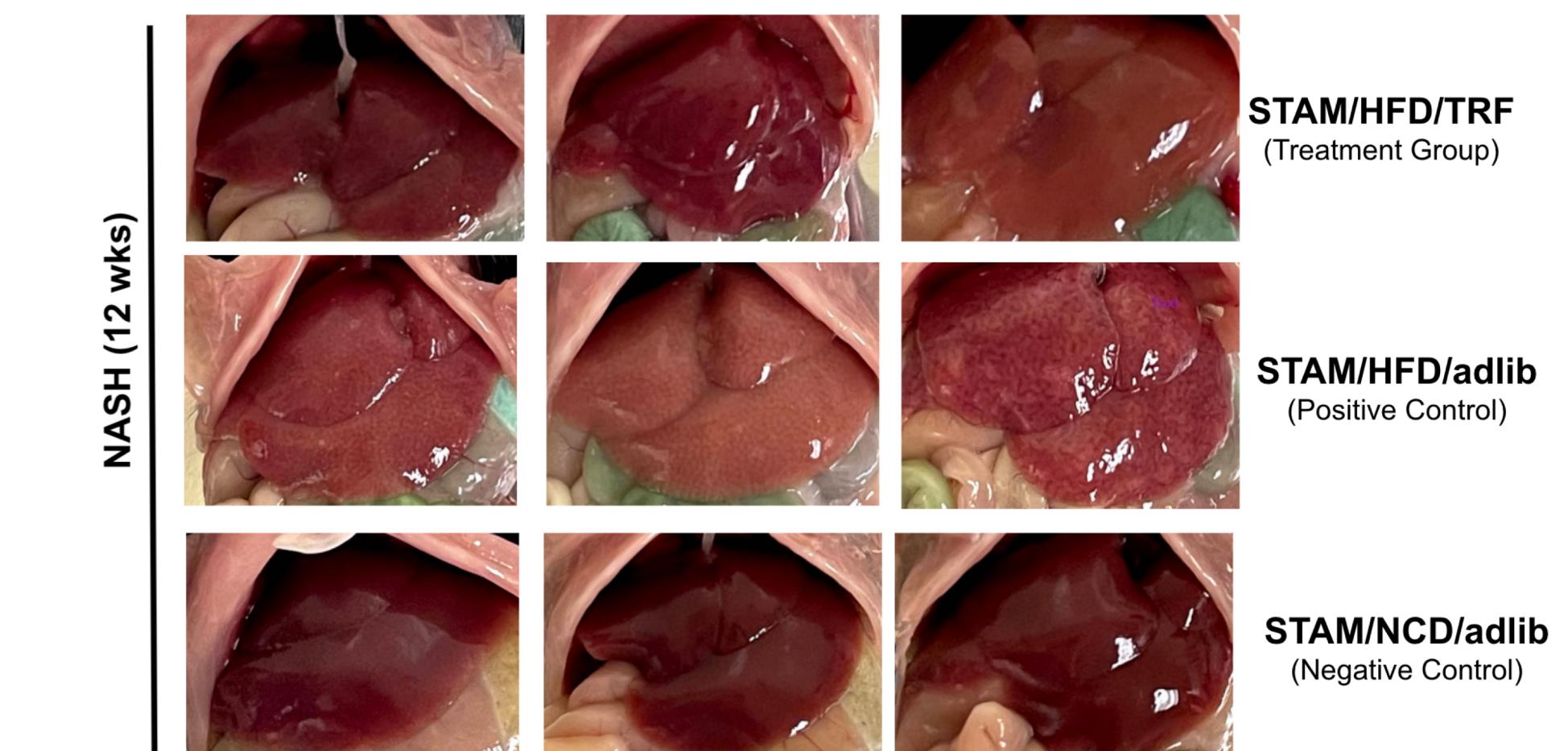


Figure 4: TRF may prevent NASH development in STAM mice



CONCLUSIONS

- STAM mice have dynamic changes in gut microbiome composition.
- Dynamic compositional changes are correlated with functional changes that increase bacterially-modified bile acids during TRF.
- TRF may prevent the development of NASH in STAM mice.
- Bile acids may be the signal linking luminal changes to host metabolic benefits in STAM mice on TRF.

REFERENCES

- Younossi, Z. M. Non-alcoholic fatty liver disease - A global public health perspective. *J. Hepatol.* 70, 531–544 (2019).
- Definition & Facts of NAFLD & NASH | NIDDK. at <https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts>.
- NASH Symptoms — American Liver Foundation. at <<https://liverfoundation.org/for-patients/about-the-liver/diseases-of-the-liver/nonalcoholic-steatohepatitis-information-center/nash-symptoms/>>.
- Saran, A. R., Dave, S. & Zarrinpar, A. Circadian rhythms in the pathogenesis and treatment of fatty liver disease. *Gastroenterology* 158, 1948–1966.e1 (2020).
- Fujii, M. et al. A murine model for non-alcoholic steatohepatitis showing evidence of association between diabetes and hepatocellular carcinoma. *Med Mol Morphol* 46, 141–152 (2013).