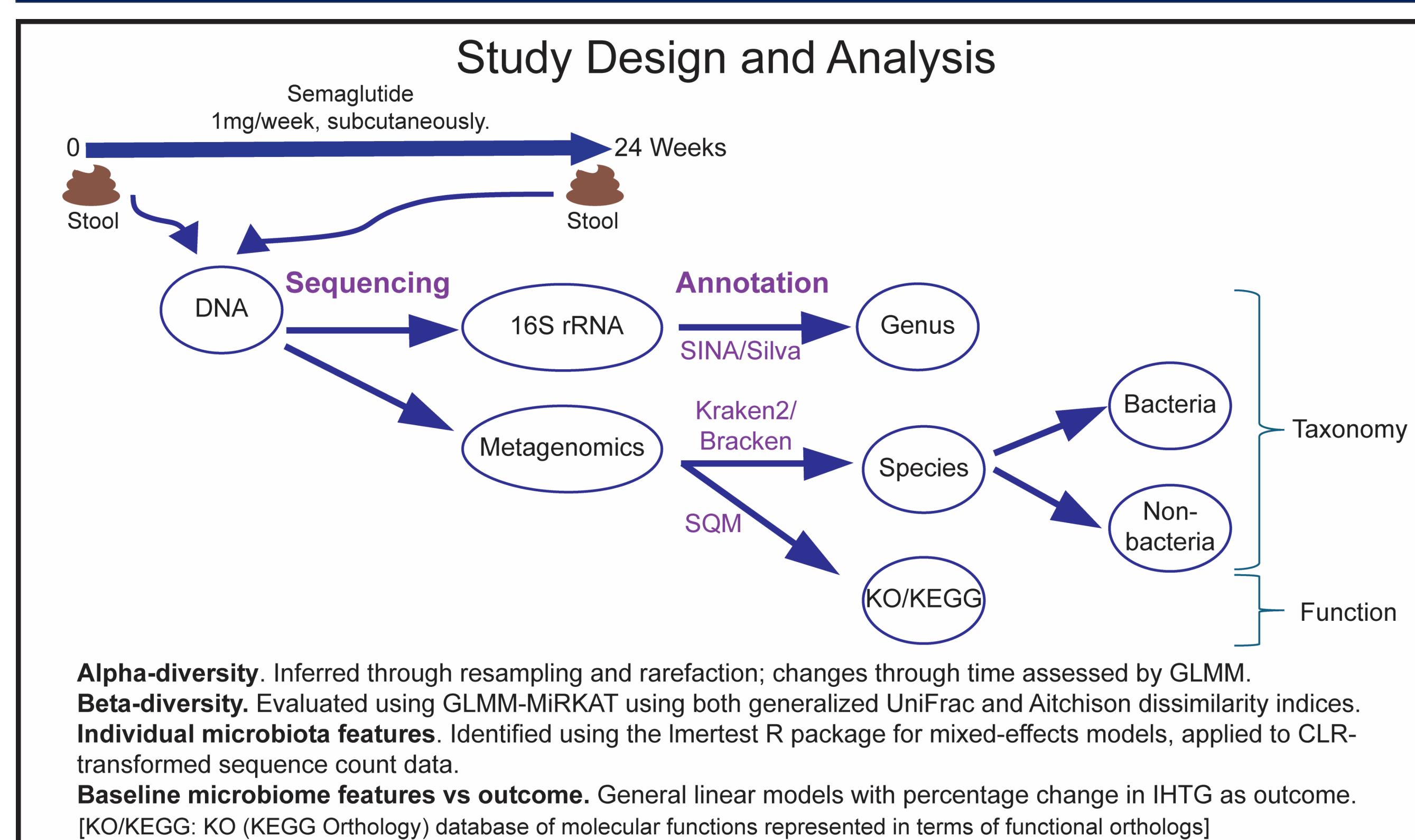


Background

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is a prevalent comorbidity in people with HIV (PWH).
- Gut microbiota profiles with lower diversity and/or altered in community structure have been variably associated with MASLD in people with and without HIV.
- Recent murine models of metabolic diseases, including MASLD, demonstrated beneficial effects of semaglutide on gut microbiota profiles and improved disease outcomes, though the effects on human gut microbiota are unknown.
- We previously demonstrated that semaglutide was highly effective in improving MASLD for PWH with clinically significant intrahepatic triglyceride (IHTG) reductions over 24 weeks (SLIM LIVER Study¹).
- Here we investigated the effects of semaglutide on the gut microbiome within the SLIM LIVER cohort.

Methods



- 51 people were enrolled into the SLIM-LIVER study [ACTG 5371] (Table 1).
- Fecal microbial communities were assessed at Week 0 (N=48) and at Week 24 (N=45).
 - Paired Week 0 and Week 24 stool samples were available from 42 participants.

Table 1. Study Participant Characteristics.

Age: 49.7 (11.0) years [mean (SD)]
Gender Identity: Cis Female 35%, Cis Male 59%, Transgender female 6%
Race and Ethnicity:
American Indian or Alaska Native 2%, Black or African American 31%
Non-Hispanic White 28%, Hispanic 37%, Multiple 2%
BMI: 35.5 (5.5) kg/m ² [mean (SD)]
Antiretroviral therapy regimen: Integrase strand inhibitor 82%

Covariate determination.

- Permutational multivariate analysis of variance (PERMANOVA) was performed on baseline microbiota features.
- Features that were found to be significantly related after univariate analysis were combined into a single multivariable PERMANOVA model: Age, Race/Ethnicity, Sex, Gender ID remained significant.
- In all analyses Age, Race/Ethnicity, and Gender ID were included as covariates.

Semaglutide alters gut microbiota profiles in PWH with MASLD. Microbiota profiles prior to treatment were associated with subsequent changes in IHTG with semaglutide.

Results

Longitudinal changes in overall microbiota composition.

- β -diversity differed between Week 0 and 24 at genus ($P=0.002$) and bacterial ($P=0.014$) and non-bacterial (archaeal/fungal/viral) species ($P=0.0059$) levels.

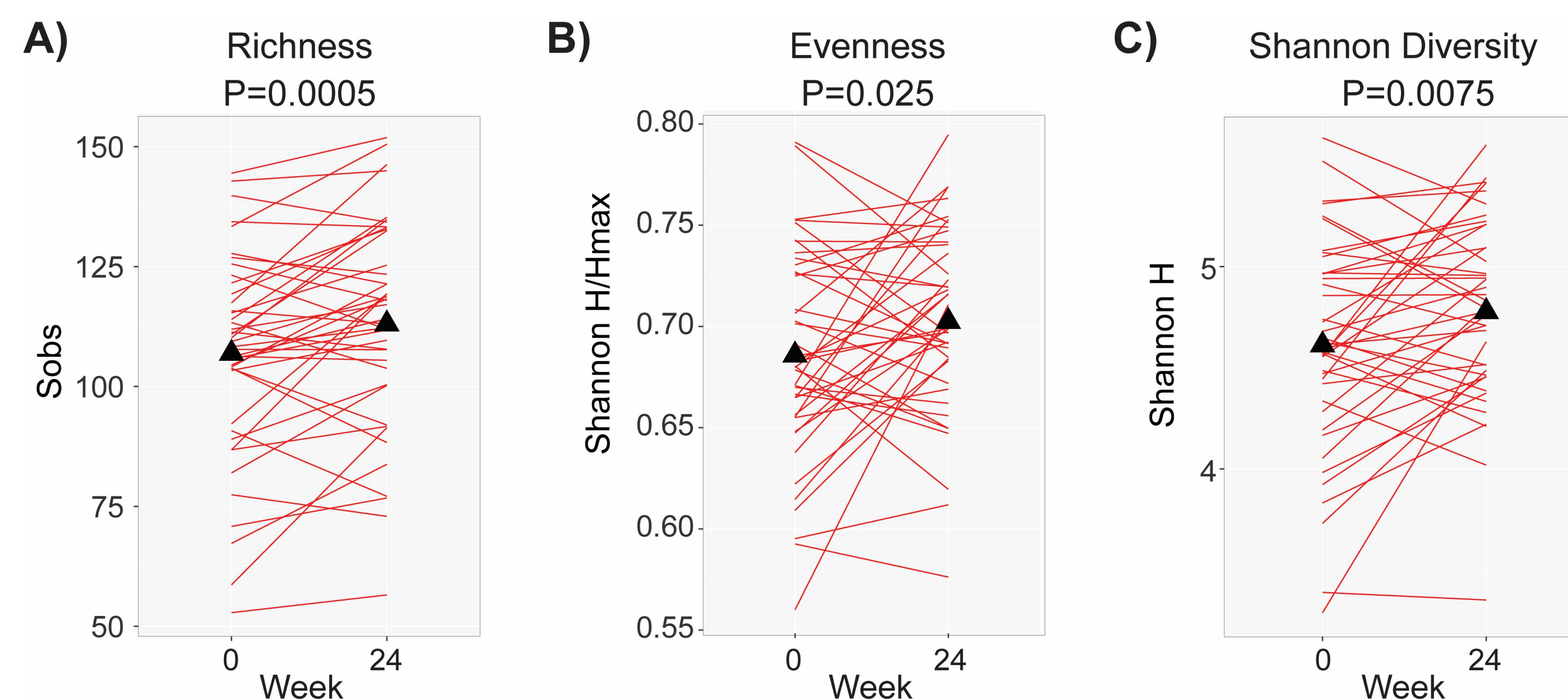


Fig. 1. Multiple measures of α -diversity were increased at 24 weeks.

Longitudinal changes in genera and species.

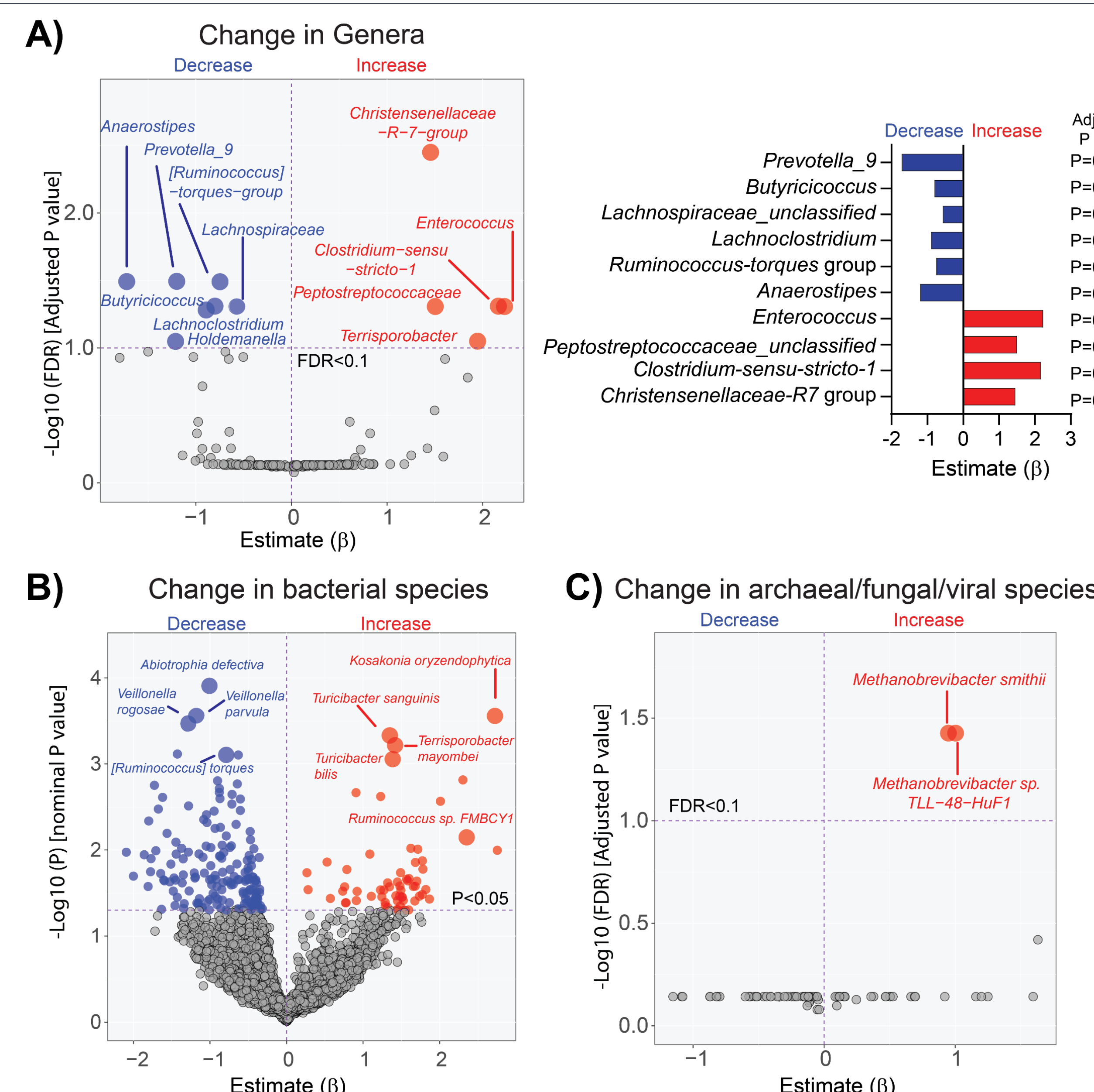


Fig. 2. At 24 weeks, increased and decreased abundances of gut-protective and potentially pathogenic bacteria were noted. Methanobrevibacter (methanogenic archaea) known to provide substrates for short chain fatty acid production were increased in abundance.

Longitudinal changes in microbial function.

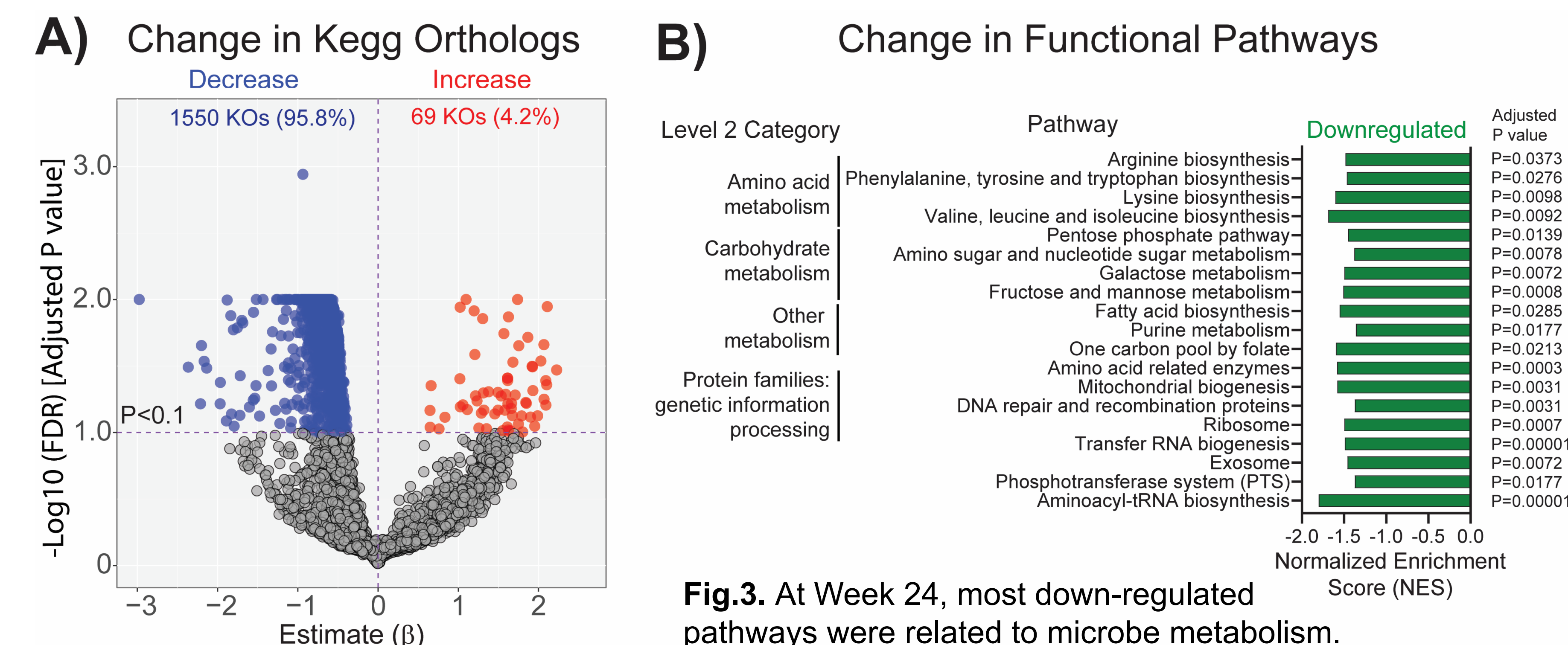


Fig.3. At Week 24, most down-regulated pathways were related to microbe metabolism.

Associations between microbiota features at Week 0 and change in percentage of IHTG at Week 24.

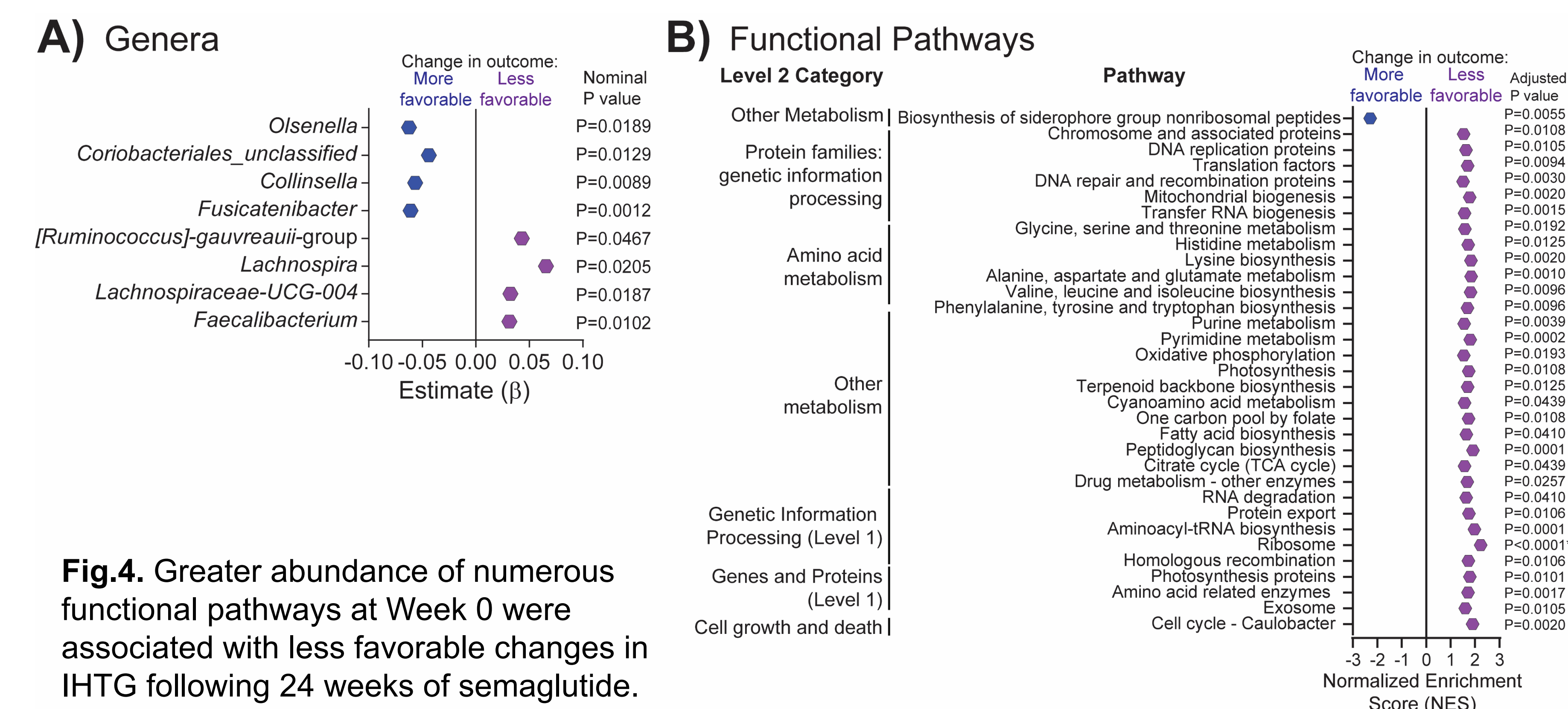


Fig.4. Greater abundance of numerous functional pathways at Week 0 were associated with less favorable changes in IHTG following 24 weeks of semaglutide.

Conclusions

- We provide first-in-human evidence that use of semaglutide alters gut microbiota profiles in PWH with MASLD. Potentially beneficial effects included increasing overall diversity and abundance of microbes associated with gut health.
- We also identified numerous microbe-related functional pathways pre-treatment that were associated with less favorable changes in IHTG.
- Our findings suggest inclusion of microbiome-targeted therapies as an adjunct to semaglutide treatment may enhance clinical outcomes in PWH with MASLD.

Acknowledgements

We thank the ACTG 5371 participants as well as the site staff and investigators for their time and dedication to this study. This work was supported by NIH (NIAID and NIA). MRI performance and reading were supported by UTHealth Houston.

References.

1. Lake, J. E. *et al. Ann. Intern. Med.* 177, 835-838 (2024).

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