Gut microbiome contributions to functional independence in older adults and centenarians

Meghan I Short[1,2], Ye Chen[1], Stacy Andersen[3], Nicole Roth[3], Tanya T Karagiannis[1,2], Sarah Bald[3], Thomas T Perls[3], Paola Sebastiani[1,2,3]

[1]Tufts Medical Center, [2]Tufts University, [3]Boston University

INTRODUCTION

Functional limitations decrease quality of life for older adults and are associated with myriad health risks. The gut microbiome is a potential therapeutic avenue for promoting functional independence among older adults, but a clearer understanding of mechanisms by which commensal gut bacteria may affect functional independence is needed.

To study the effects of microbes on independent functioning in older adults, I analyzed data from an ongoing cohort study, Integrative Longevity Omics (ILO), which so far has 220 shotgun metagenomics samples of the gut microbiome in centenarians and their offspring. By examining centenarians and their families, I am leveraging a population known to be enriched in protective factors for longevity and increased health span that have translational potential for mitigating age-related symptoms in older adults generally.

METHODS

Metagenomics samples were profiled using MetaPhlAn 4. I tested for associations between species-level microbial alpha diversity (Shannon index) and measures of functioning including activities of daily living (ADLs, scored 0 - 6) and instrumental activities of daily living (IADLs; modified Lawton scale, scored 0 - 1) via linear regression adjusting for age, sex, and education. Higher ADL and IADL scores indicate greater functional independence.

I visualized species-level microbial beta diversity using Principal Coordinates Analysis applied to Bray-Curtis dissimilarities among samples' microbial profiles, and I tested for associations with ADLs and IADLs via permutational analysis of variance (PERMANOVA).

I measured associations between relative abundances of all taxa (Phylum through Species) with ADLs and IADLs using linear regression with generalized estimating equations (GEE) to account for within-family correlations, adjusting for age, sex, and education. Relative abundances were log-transformed to reduce skewness.

RESULTS

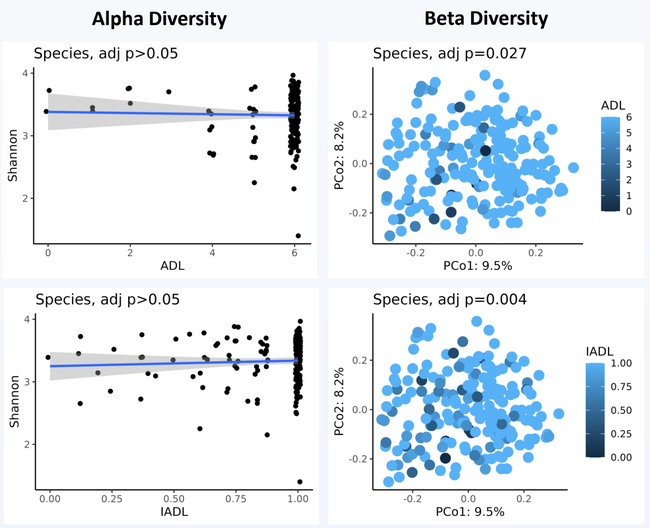

Figure 1: Left: Jittered scatterplots of Shannon alpha diversity index plotted against ADLs (top) and IADLs (bottom). P values are from GEE adjusted for age, sex, and education; lines and confidence bands are from unadjusted linear regression models. Right: Principal Coordinate Analysis plots of Bray-Curtis dissimilarities, colored by ADLs (top) and IADLs (bottom). P values are from PERMANOVA adjusted for age, sex, and education.

Taxon	Estimate	P-value	FDR
Phylum			
k__Archaea_p__Euryarchaeota	-0.573	0.0036	0.043
k__Bacteria_p__Lentisphaerae	-0.540	0.0081	0.049
Class			
k__Bacteria_p__Proteobacteria_c__Deltaproteobacteria	-0.386	0.0011	0.024
k__Archaea_p__Euryarchaeota_c__Methanobacteria	-0.573	0.0036	0.039
Order			
k__Bacteria_p__Actinobacteria_c__Coriobacteriia_o__Coriobacteriales	-0.536	0.0001	0.0043
k__Bacteria_p__Proteobacteria_c__Deltaproteobacteria _o__Desulfovibrionales	-0.386	0.0011	0.021
k__Archaea_p__Euryarchaeota_c__Methanobacteria _o__Methanobacteriales	-0.573	0.0036	0.045
Family			
k__Bacteria_p__Actinobacteria_c__Coriobacteriia_o__Coriobacteriales_ f__Coriobacteriaceae	-0.595	0.0001	0.0078
k__Bacteria_p__Proteobacteria_c__Deltaproteobacteria _o__Desulfovibrionales_f__Desulfovibrionaceae	-0.386	0.0011	0.042

Table 1: Taxa associated with ADLs at FDR<0.05. Estimates represent the log-fold-change of the relative abundance associated with a 1-unit increase in ADLs, adjusting for age, sex, and education. No associations between taxa and IADLs were statistically significant.

Species-level alpha diversity was not associated with ADLs or IADLs via linear regression adjusting for age, sex, and education (**Fig. 1, left**).

Species-level beta diversity (Bray-Curtis dissimilarity) was associated with ADLs (p=0.03) and IADLs (p=0.004) adjusting for age, sex, and education using PERMANOVA (**Fig. 1, right**).

Several taxa were associated with ADLs, including families *Coriobacteriaceae* (β=-0.595; FDR q=0.008) and *Desulfovibrionaceae* (β=-0.386; FDR q=0.04). A one-unit increase in ADLs was associated with a 44% decrease in *Coriobacteriaceae* and a 32% decrease in *Desulfovibrionaceae* relative abundance, adjusting for age, sex, and education (**Table 1, Fig. 2**). No taxa were associated with IADLs at FDR<0.05.

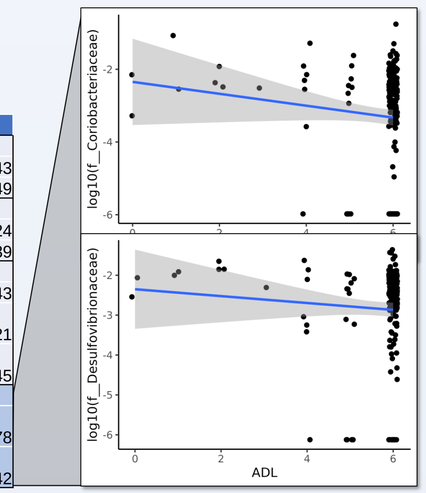

Figure 2: Jittered scatterplots of log10-relative-abundances of ADL-associated microbial families plotted against ADL values. Lines and confidence bands are from unadjusted linear regression models.

DISCUSSION

To our knowledge, this is the first investigation of metagenomic gut microbial features associated with functional independence in older adults. We observed associations between microbial beta diversity and measures of functioning ADLs and IADLs, independent from effects of age. Microbial species alpha diversity was not associated with functional independence.

Coriobacteriaceae and *Desulfovibrionaceae,* which were more abundant in those with lower ADL scores, have previously documented associations with inflammation, poor diet, and liver and cardiovascular disease (1-4).

Future analyses will incorporate domains of physical frailty as phenotypes of interest and use an expanded set of metagenomics and metabolomics samples (currently being processed) that will double the current dataset. Analyses will be replicated in a published metagenomics dataset from a longevous cohort with ADLs/IADLs available.

REFERENCES

1. van Soest APM, Hermes GDA, Berendsen AAM, et al. Associations between Pro- and Anti-Inflammatory Gastro-Intestinal Microbiota, Diet, and Cognitive Functioning in Dutch Healthy Older Adults: The NU-AGE Study. *Nutrients*. 2020;12(11):3471. doi:10.3390/nu12113471
2. Ma E, Maskarinec G, Lim U, et al. Long-term association between diet quality and characteristics of the gut microbiome in the multiethnic cohort study. *British Journal of Nutrition*. 2022;128(1):93-102. doi:10.1017/S0007114521002968
3. Astbury S, Atallah E, Vijay A, Aithal GP, Grove JI, Valdes AM. Lower gut microbiome diversity and higher abundance of proinflammatory genus Collinsella are associated with biopsy-proven nonalcoholic steatohepatitis. Gut Microbes. 2020;11(3):569-580. doi:10.1080/19490976.2019.1681861
4. Zhu X, Cai J, Wang Y, Liu X, Chen X, Wang H, Wu Z, Bao W, Fan H, Wu S. A High-Fat Diet Increases the Characteristics of Gut Microbial Composition and the Intestinal Damage Associated with Non-Alcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*. 2023; 24(23):16733. https://doi.org/10.3390/ijms242316733

ACKNOWLEDGEMENTS

Funding for this study was provided by a Research Education Core grant from the Boston Claude D. Pepper Older Americans Independence Center.

ILO Study: NIA UH2AG064704.

Contact: Meghan.Short@tuftsmedicine.org