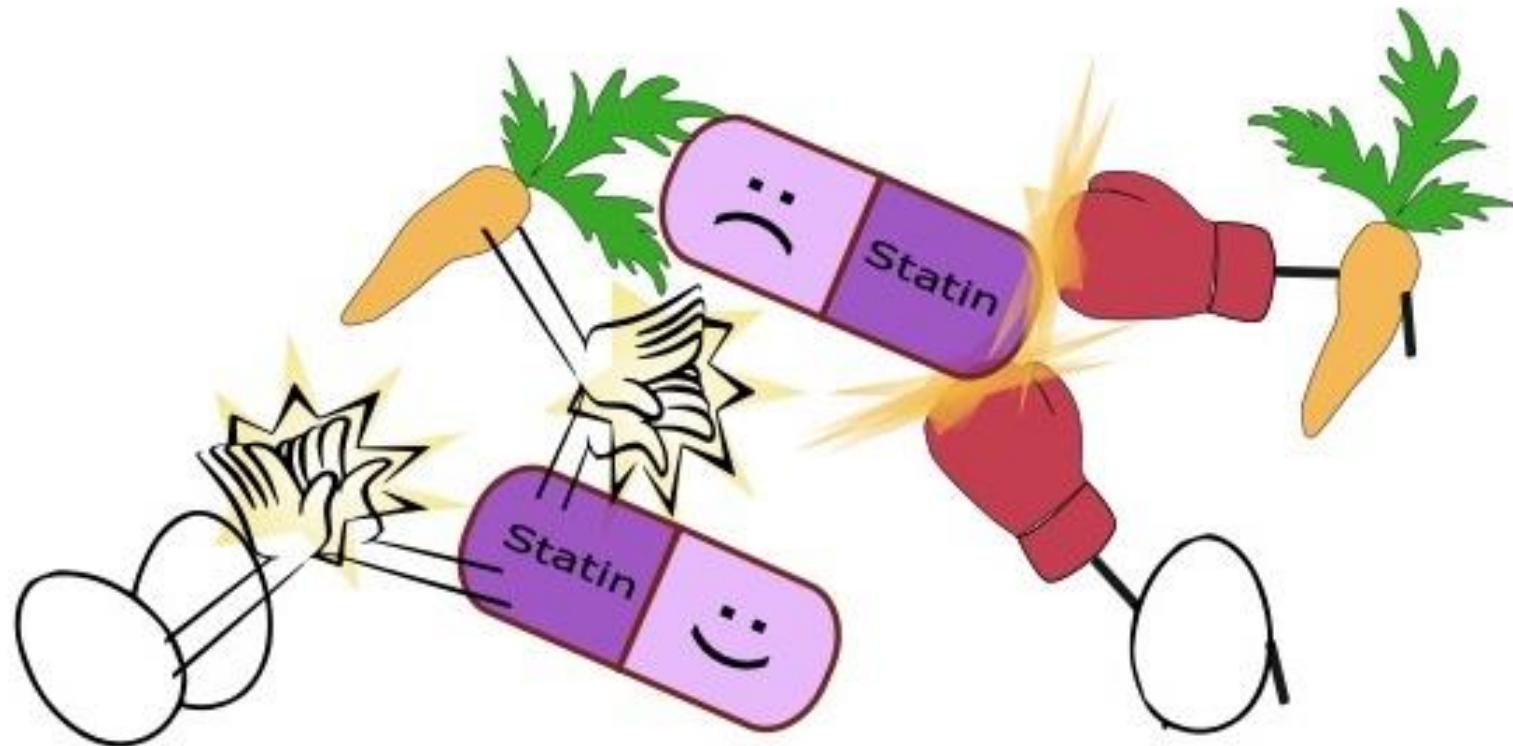


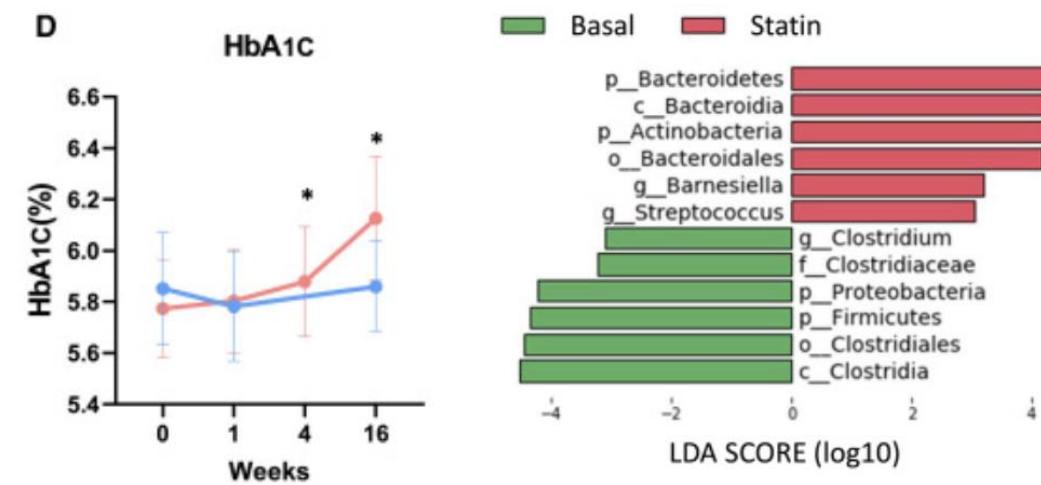
Statin Efficacy for Varying Diets and Gut Microbes

Anika O'Brian



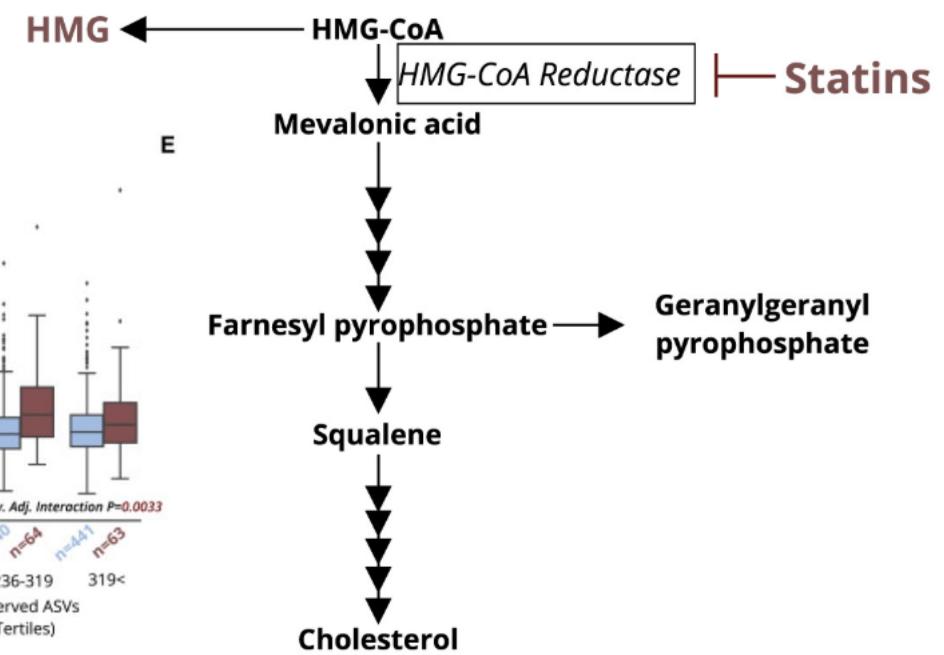
How do we measure Statin Efficacy?

- Understanding factors that enhance or inhibit their effectiveness can lead to **better patient outcomes**
- Explore **discrepancy in patient outcomes**: why do some patients benefit more than others?
- Minimize side effects**: insulin resistance/diabetes, muscle soreness
- Apply to other medications for **microbiome-informed drug therapies**

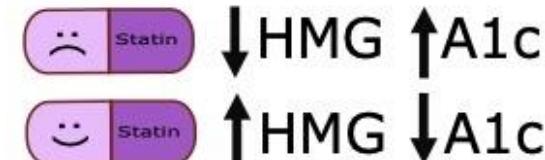


<https://www.sciencedirect.com/science/article/pii/S1550413123005053?via%3Dihub>

Goal: Lower LDL cholesterol to prevent heart disease with out side effects

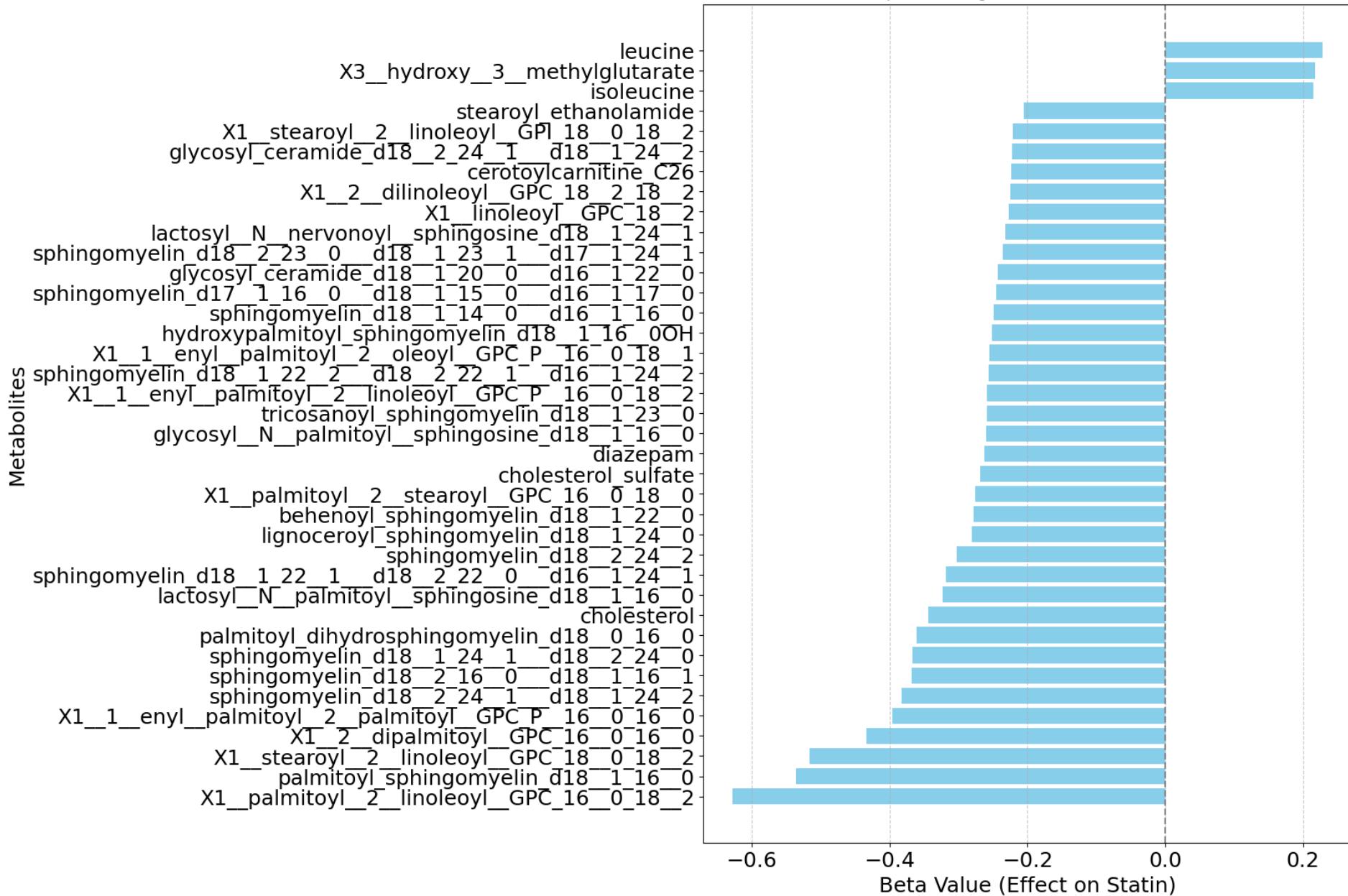


<https://www.sciencedirect.com/science/article/pii/S2000024020001700?via%3Dihub>

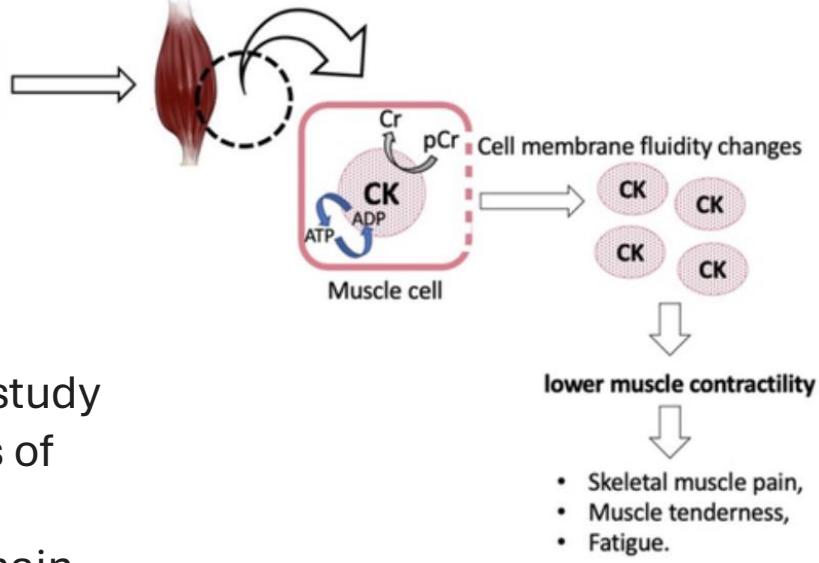
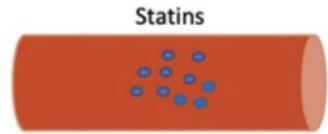


Statin ~ C(Gender) + C(Nationality) + seq_depth + C(Status) + Metabolite

Creatine was also significant but here we're only looking at beta values $> |0.2|$



Creatin



Sphingomyelin is a type of lipid found in cell membranes → influence cholesterol distribution, serve as precursors for bioactive sphingolipids involved in cell signaling and apoptosis.

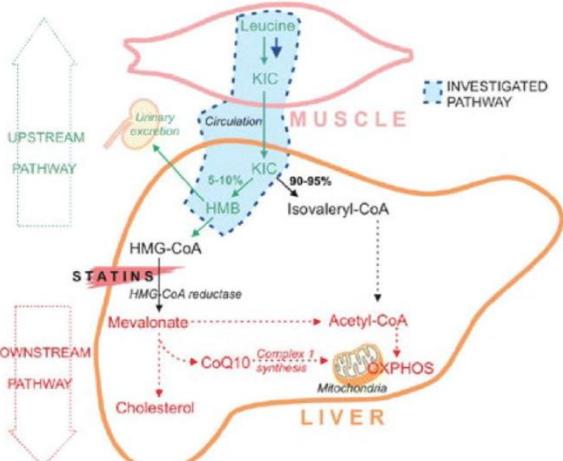
Diazepam

Simvastatin(a statin) might reduce the anxiolytic effect and the bioavailability of diazepam
 → Lower diazepam, lower liver function
 → Statin decreases liver function

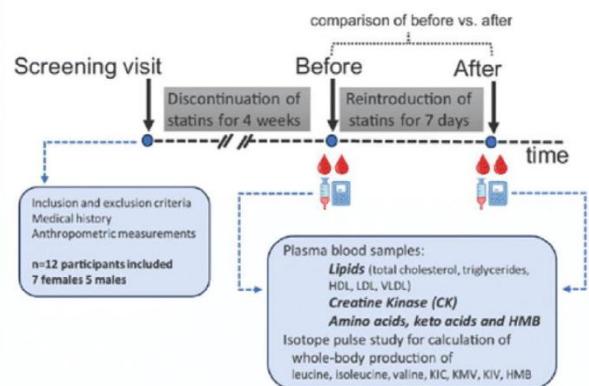
Leucine

- Purpose was to study metabolic causes of statin-induced myopathy but remain uncertain
- Upstream inhibition of statins reduces the whole body turnover of leucine
- Statins does not change the turnover of the anabolic agent of HMB.

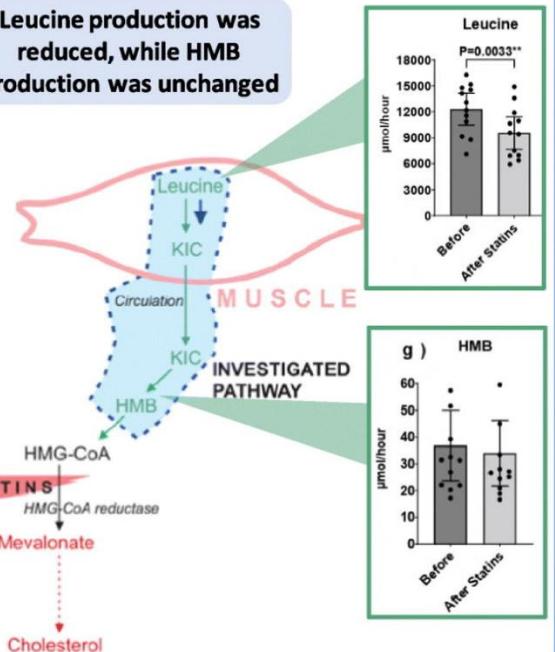
- The underlying causes of statin induced myopathy are uncertain
- Upstream effect of blocking HMG-CoA on leucine metabolism has not been investigated



- Healthy older participants were included
- Statin treatment was discontinued (4 weeks) and then reintroduced for 7 days
- Amino acid metabolism was investigated with isotope pulse methodology

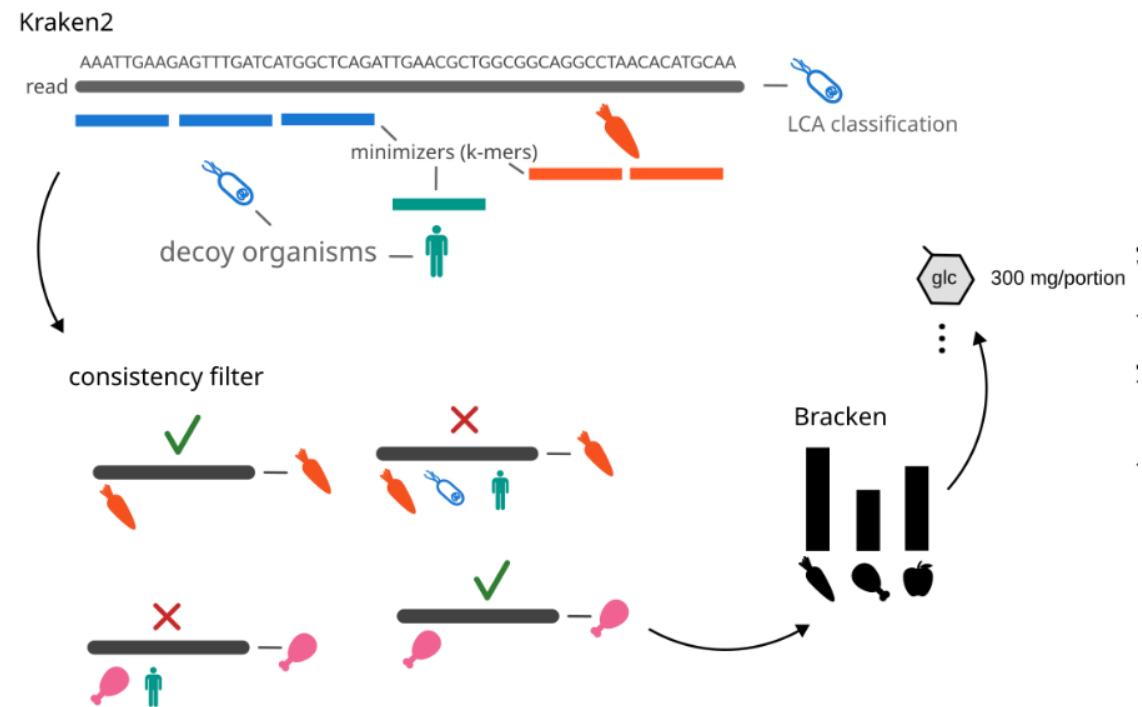
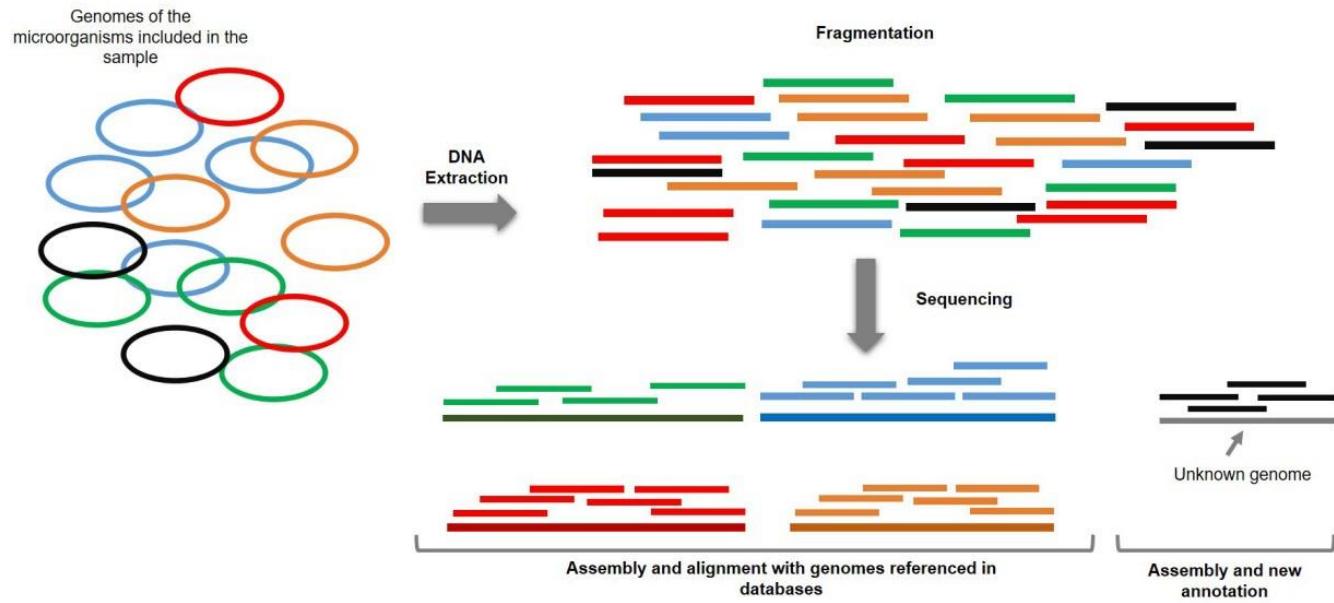


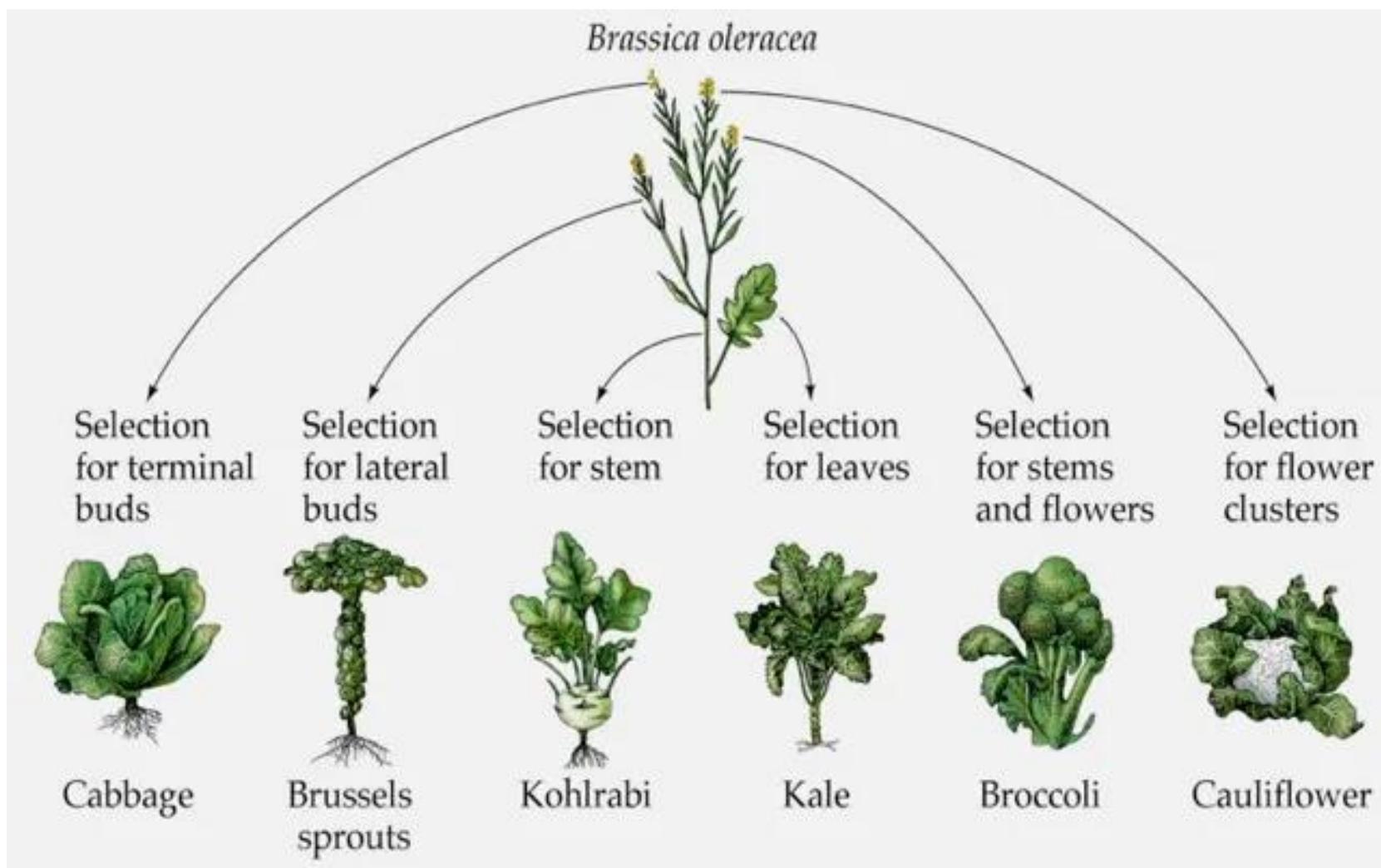
Leucine production was reduced, while HMB production was unchanged



[Source](#) , [Source2](#)

How Medi Works

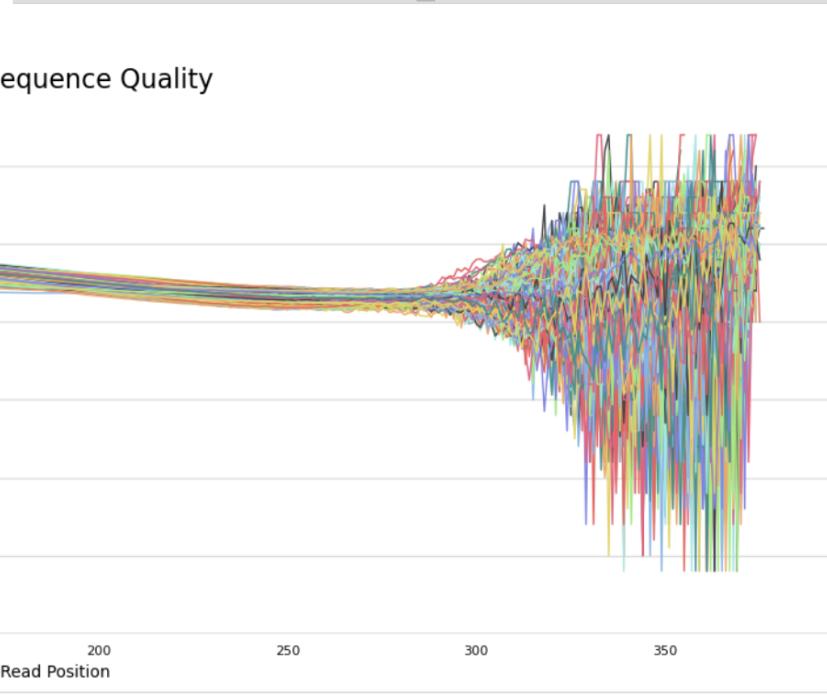
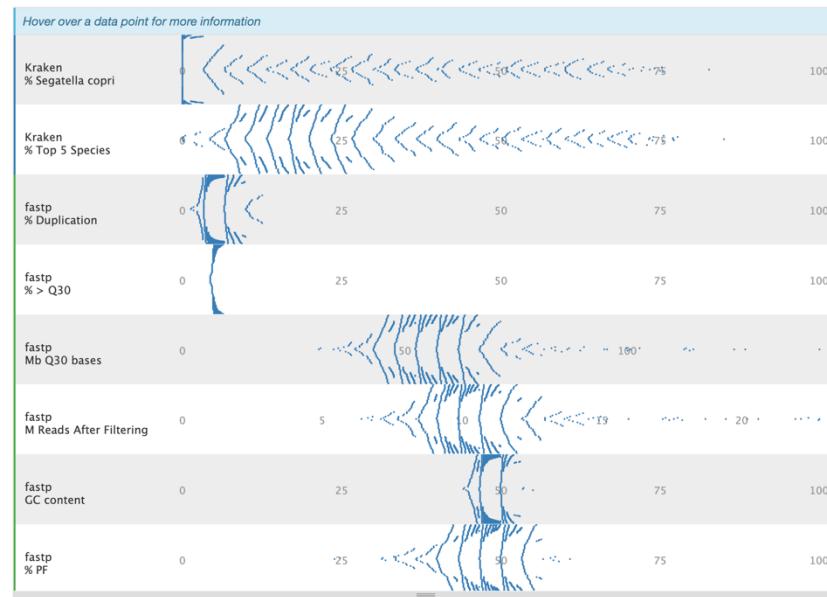
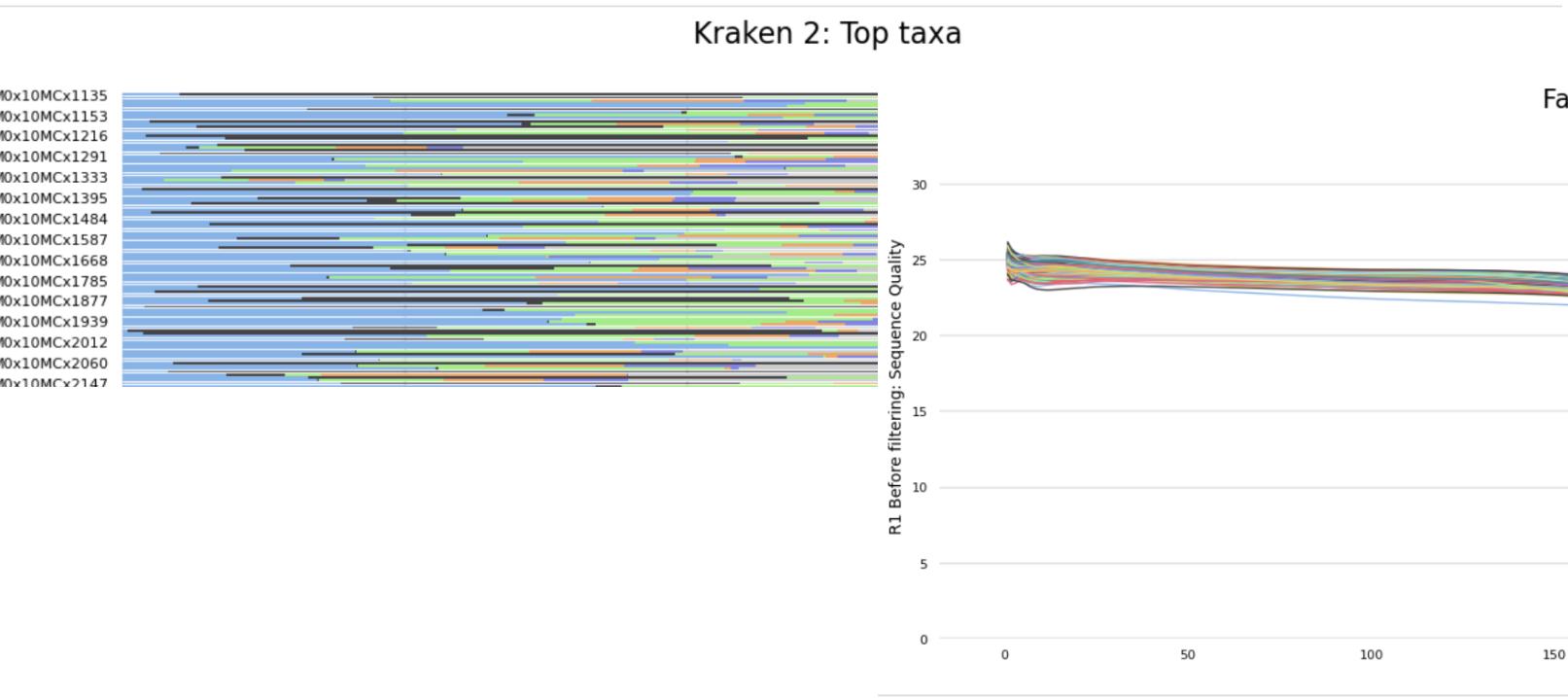




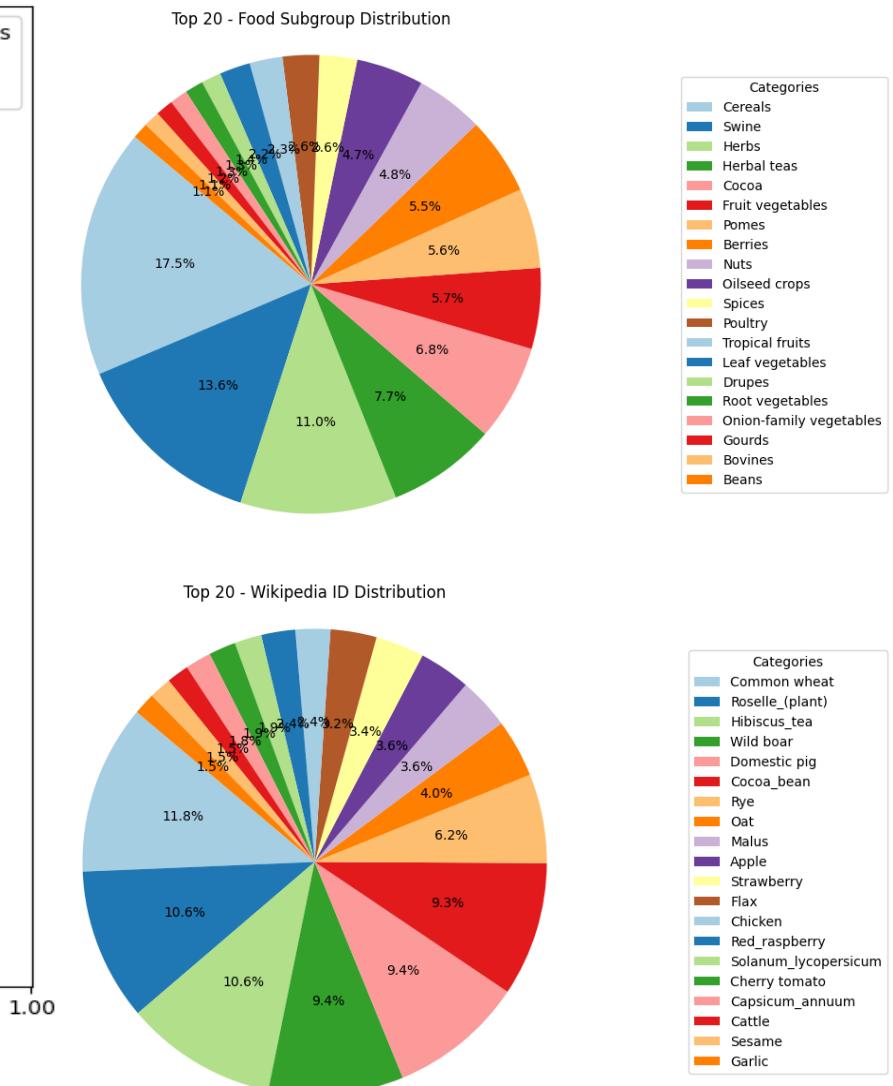
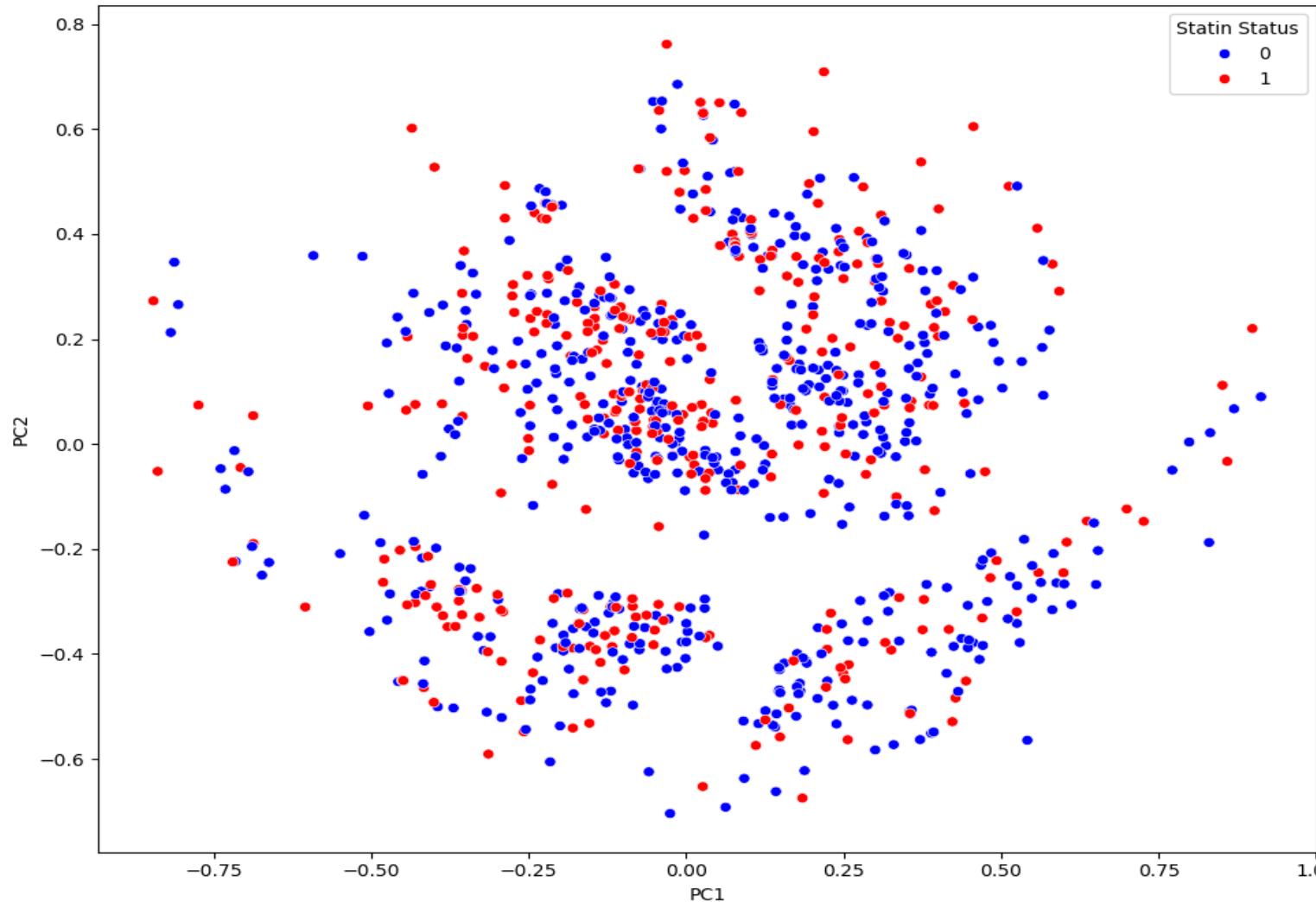
- In a sample with two foods of differing abundance, MEDI over assigns reads to the more abundant food at the expense of the less abundant food
- MEDI cannot reliably identify fish and shellfish
- MEDI requires foods to survive the journey into the colon, which biases the data towards plant-derived foods and less-processed foods
- Many highly processed foods do not contain DNA signatures (eg. processed sugars, cooking oils)
- MEDI still suffers from existing food databases having a Eurocentric bias

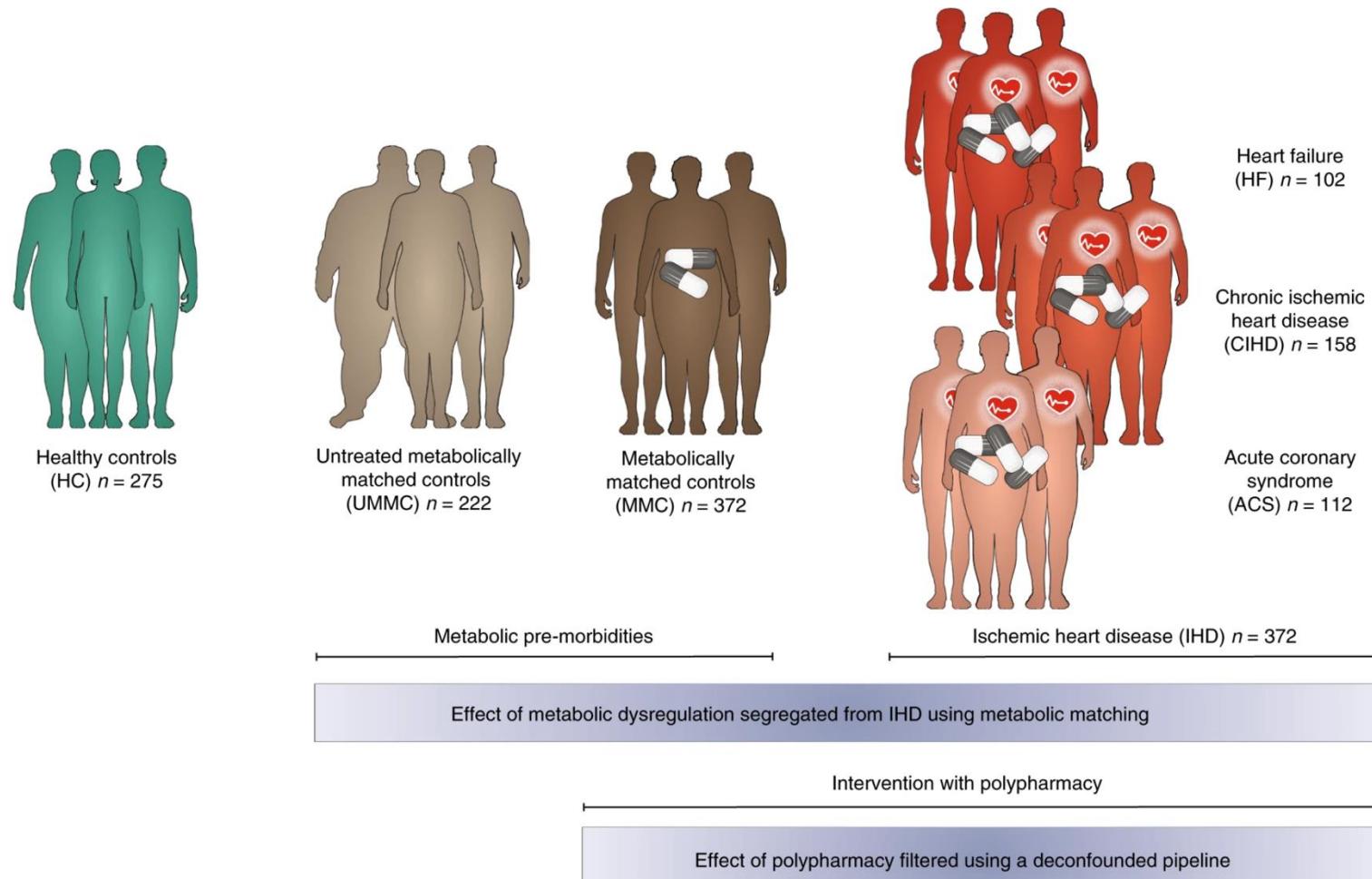
Running Medi on Metacardis

PRJEB37249, PRJEB38742,

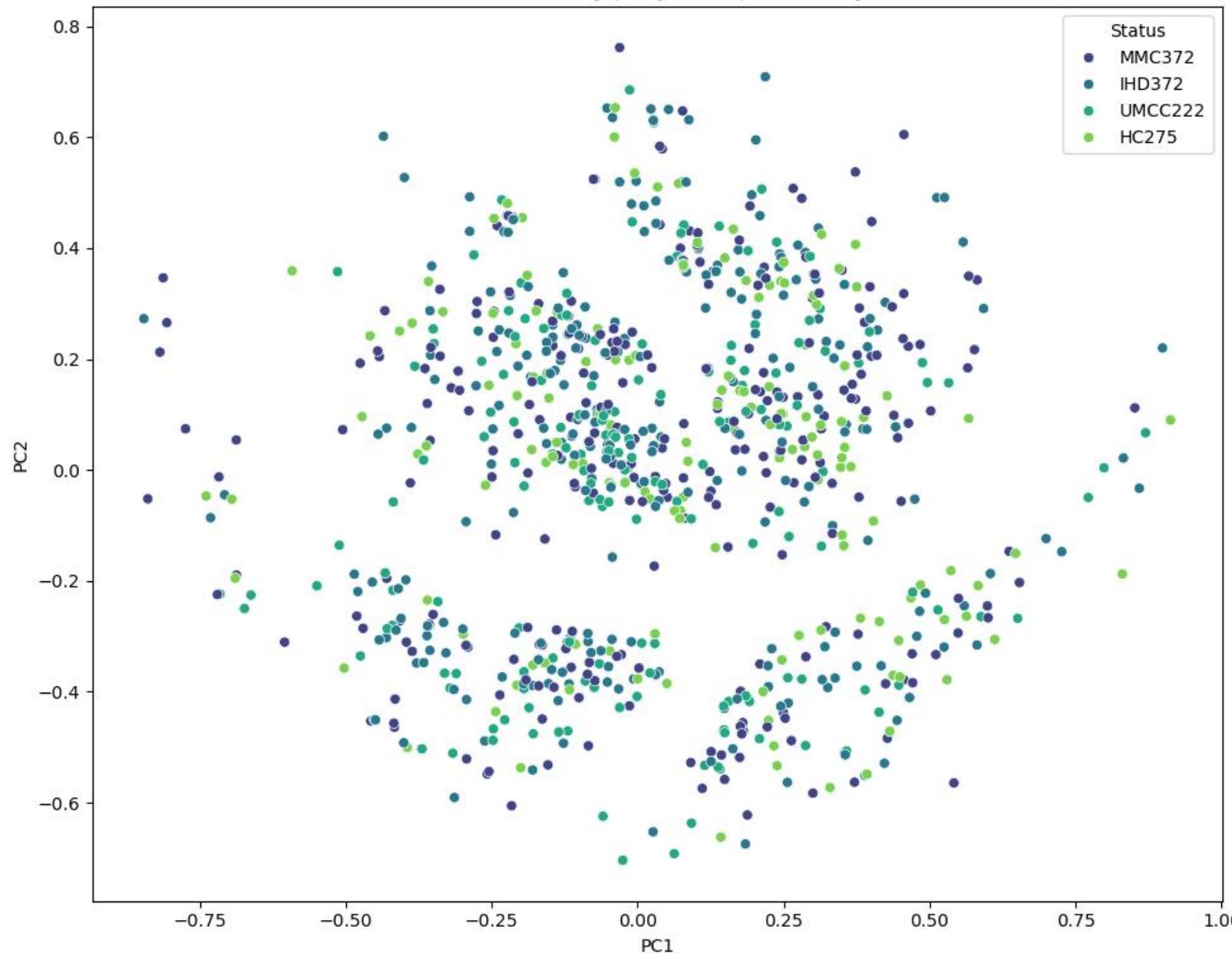


Diet Beta Diversity using Bray-Curtis Dissimilarity Matrix on full medi output food sub-groups n=1,906





PCoA of Diet Diversity (Bray-Curtis) Colored by Status



Summary Statistics by Status:

Status: HC275

Number of individuals: 152

Average PC1: 0.0870

Average PC2: 0.0273

Status: IHD372

Number of individuals: 262

Average PC1: 0.0197

Average PC2: 0.0393

Status: MMC372

Number of individuals: 279

Average PC1: 0.0424

Average PC2: 0.0081

Status: UMCC222

Number of individuals: 177

Average PC1: 0.0082

Average PC2: -0.0505

ANOVA test for PC1 by Status:

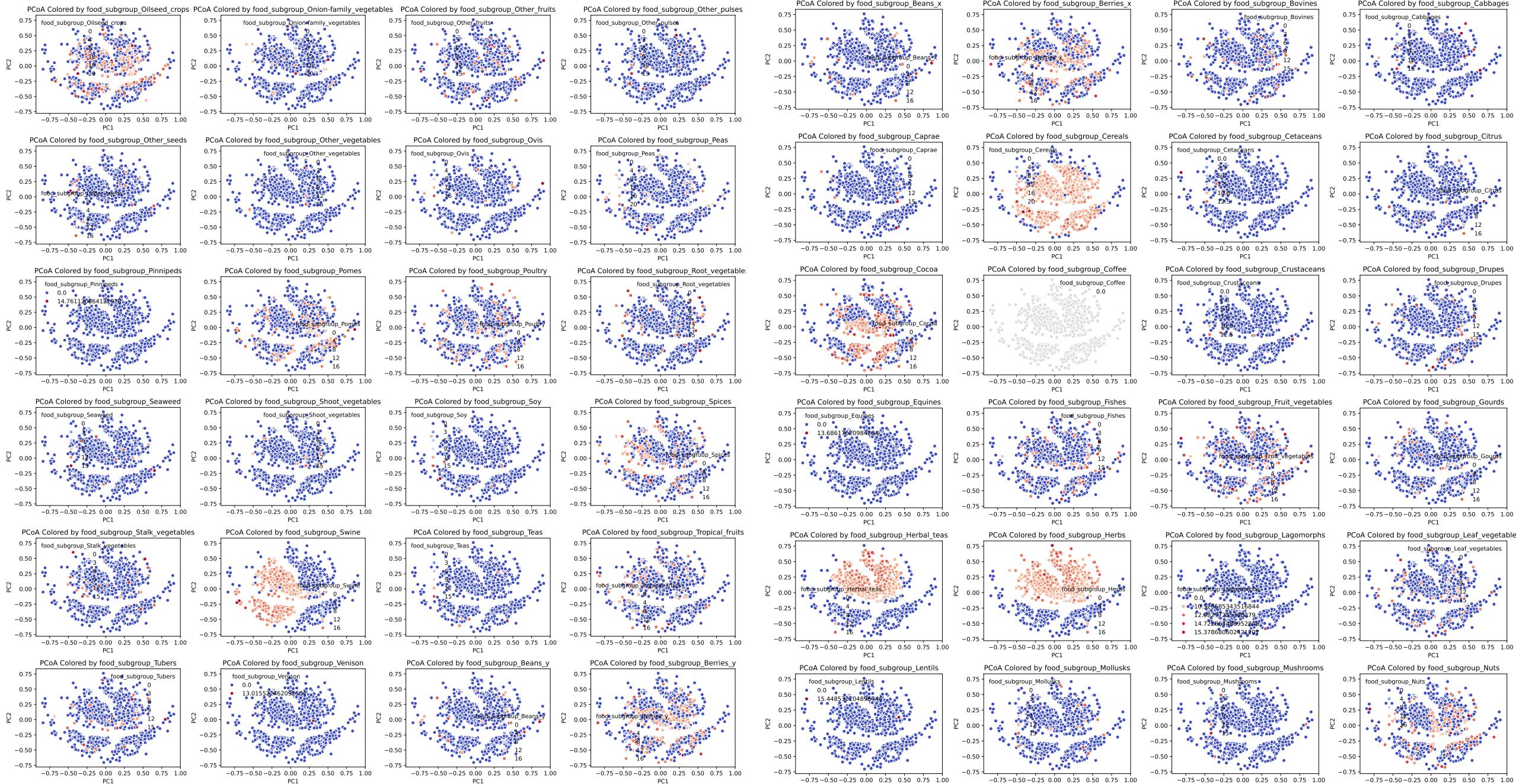
F-statistic: 2.3071

p-value: 0.0752

Background

Methods

Results

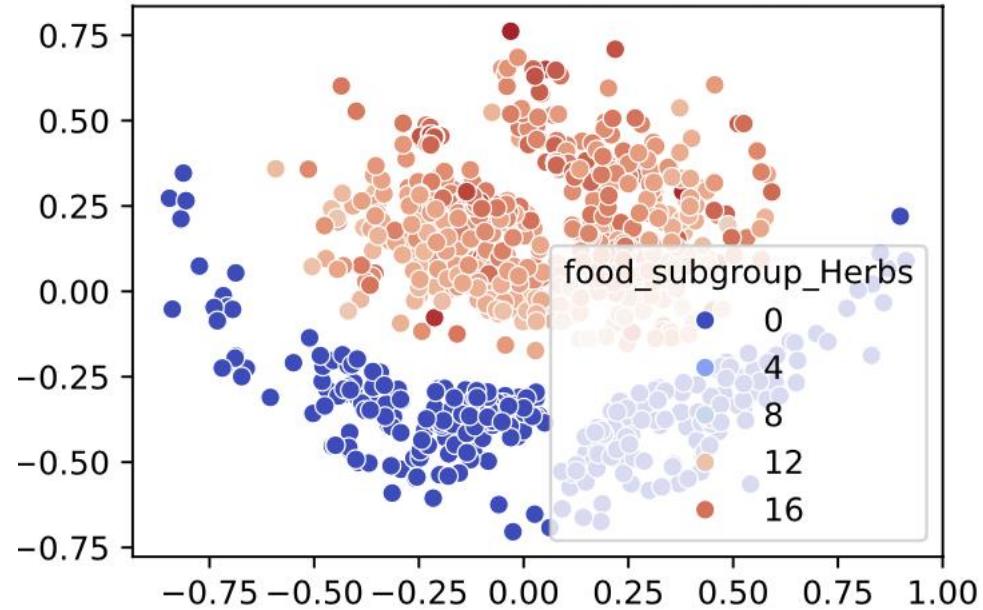


Background

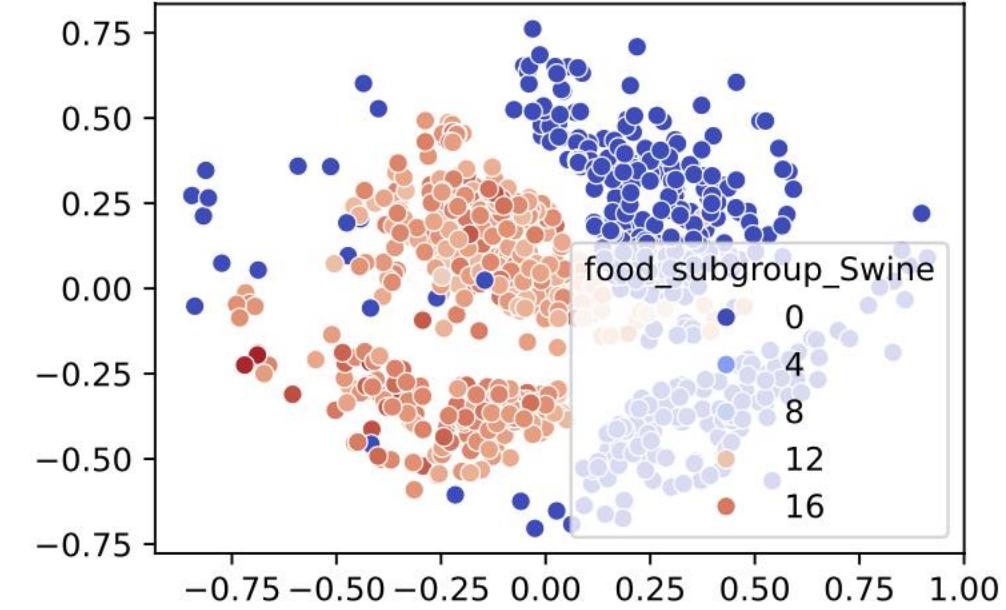
Methods

Results

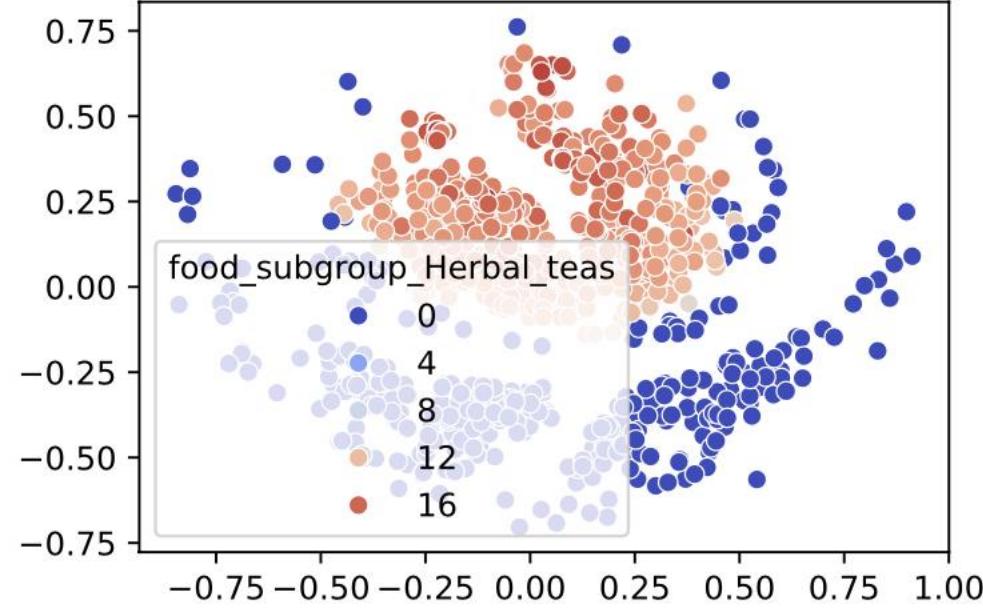
PCoA Colored by food_subgroup_Herbs



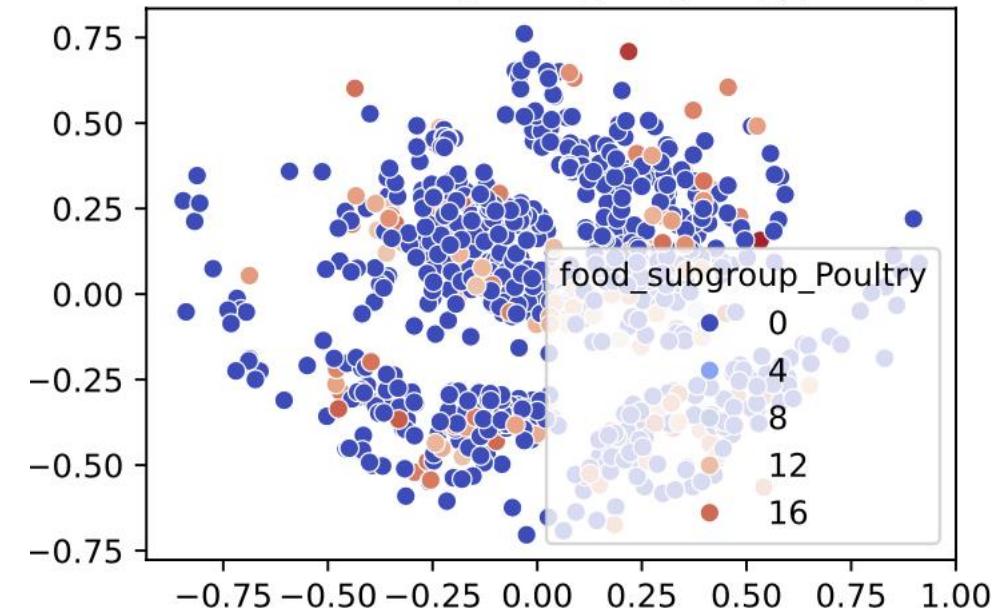
PCoA Colored by food_subgroup_Swine



PCoA Colored by food_subgroup_Herbal_teas



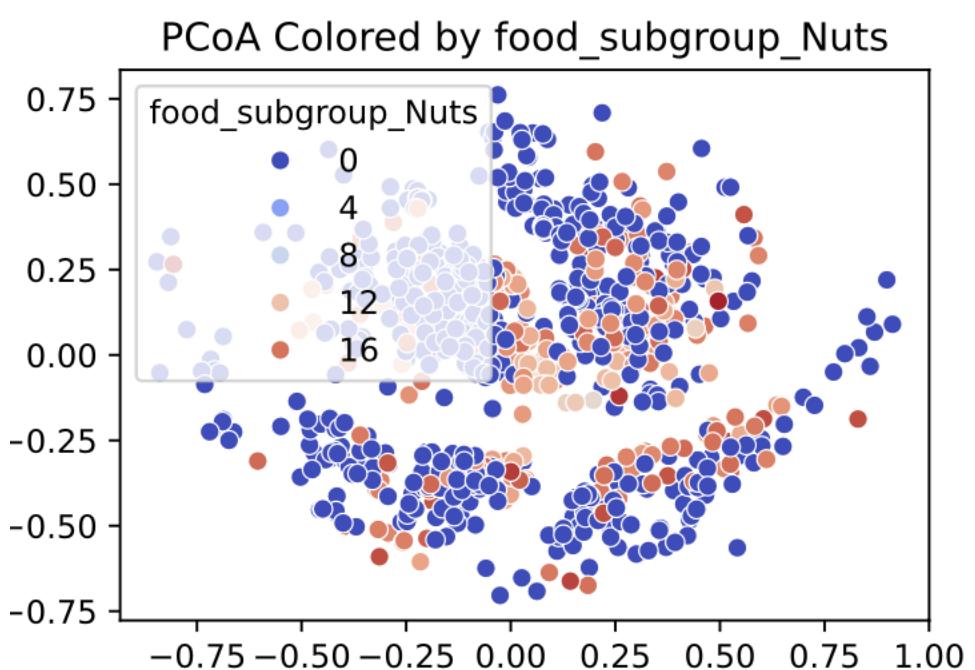
PCoA Colored by food_subgroup_Poultry



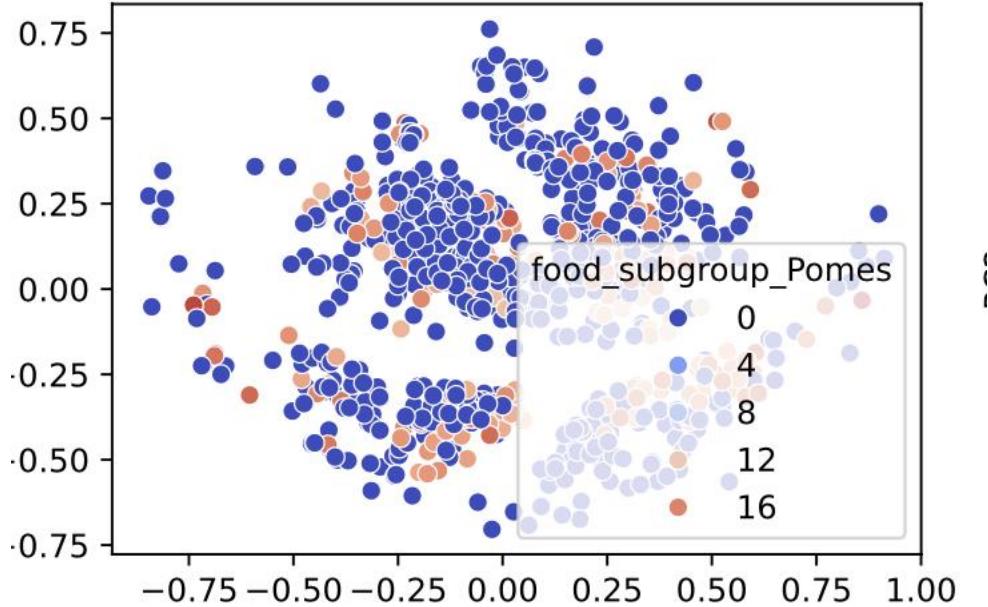
Background

Methods

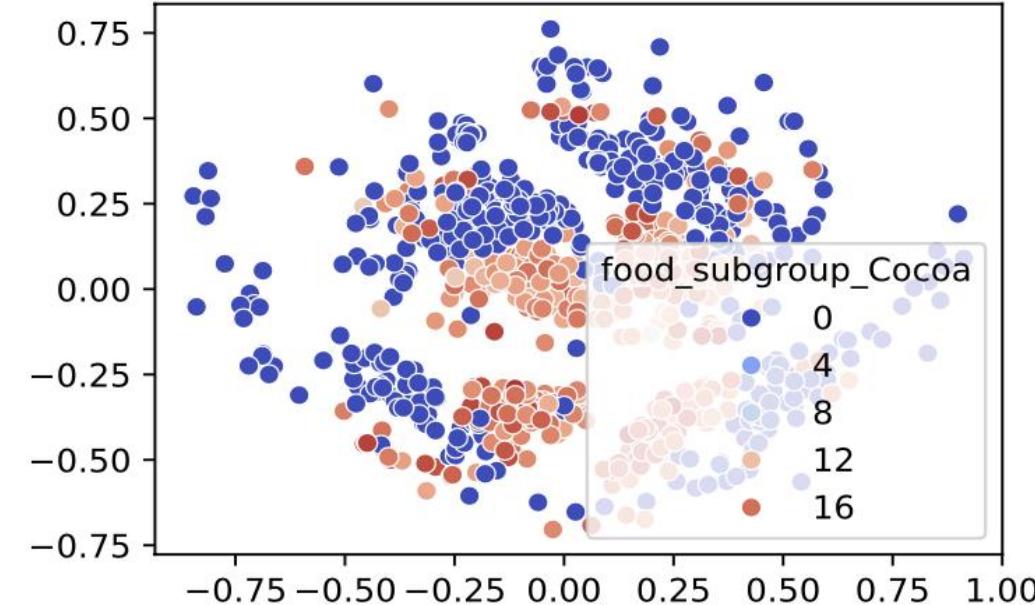
Results



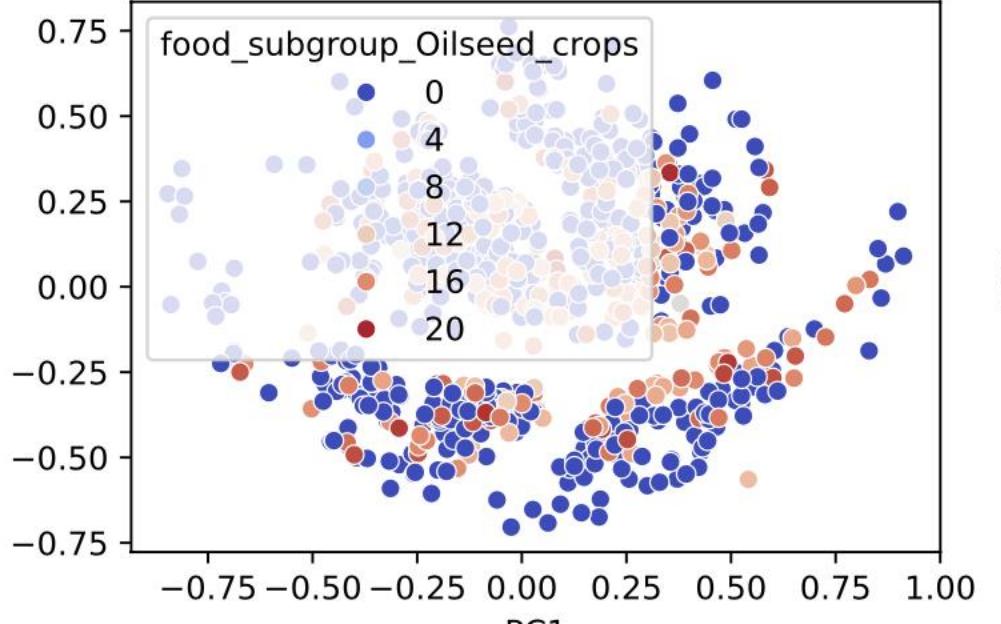
PCoA Colored by food_subgroup_Pomes

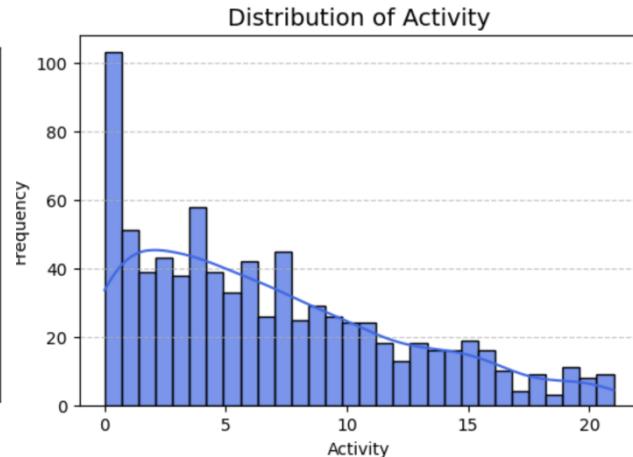
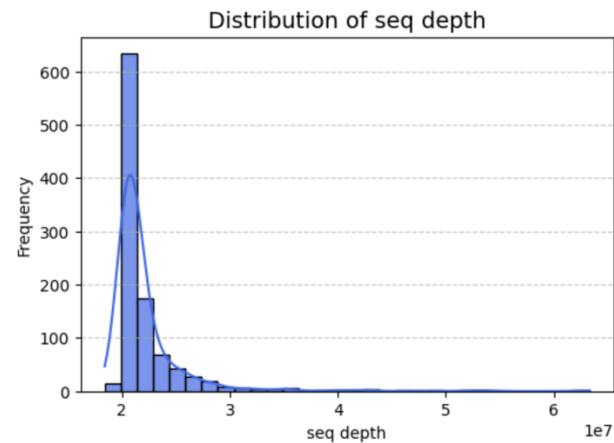
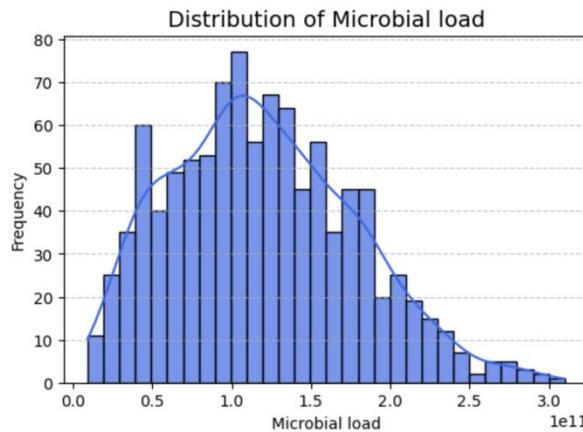
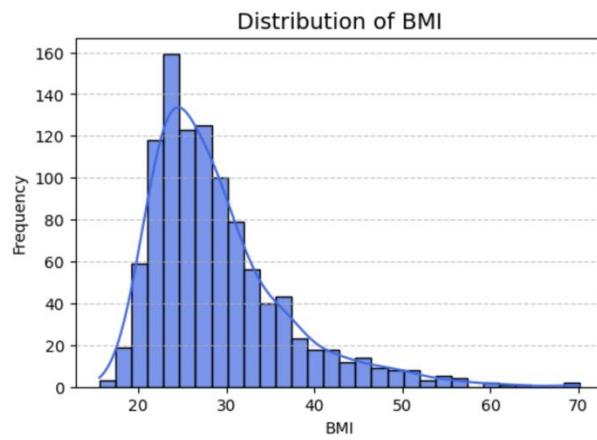
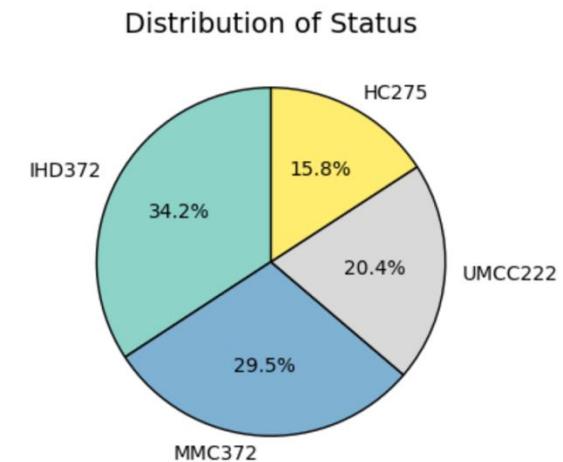
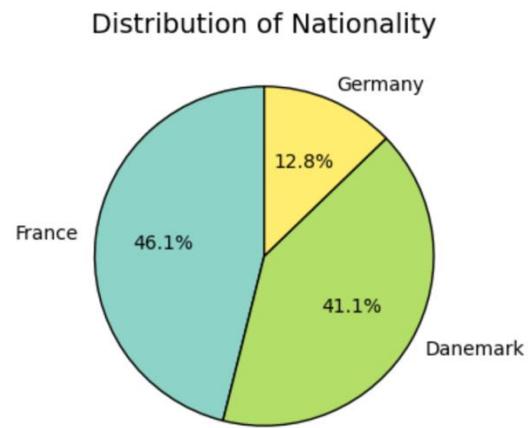
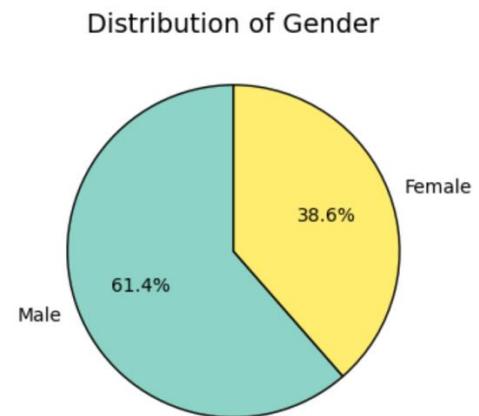
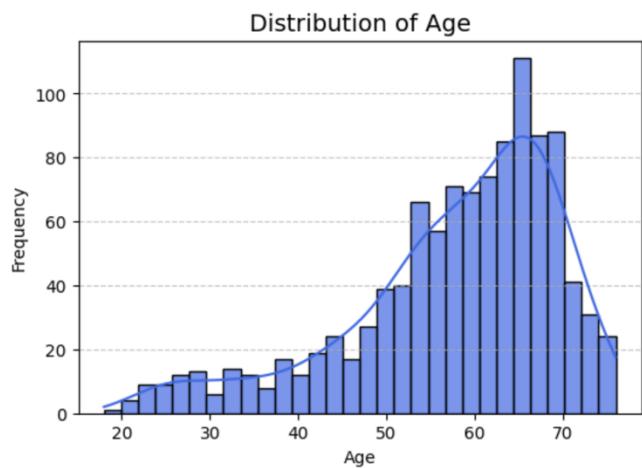


PCoA Colored by food_subgroup_Cocoa



PCoA Colored by food_subgroup_Oilseed_crops



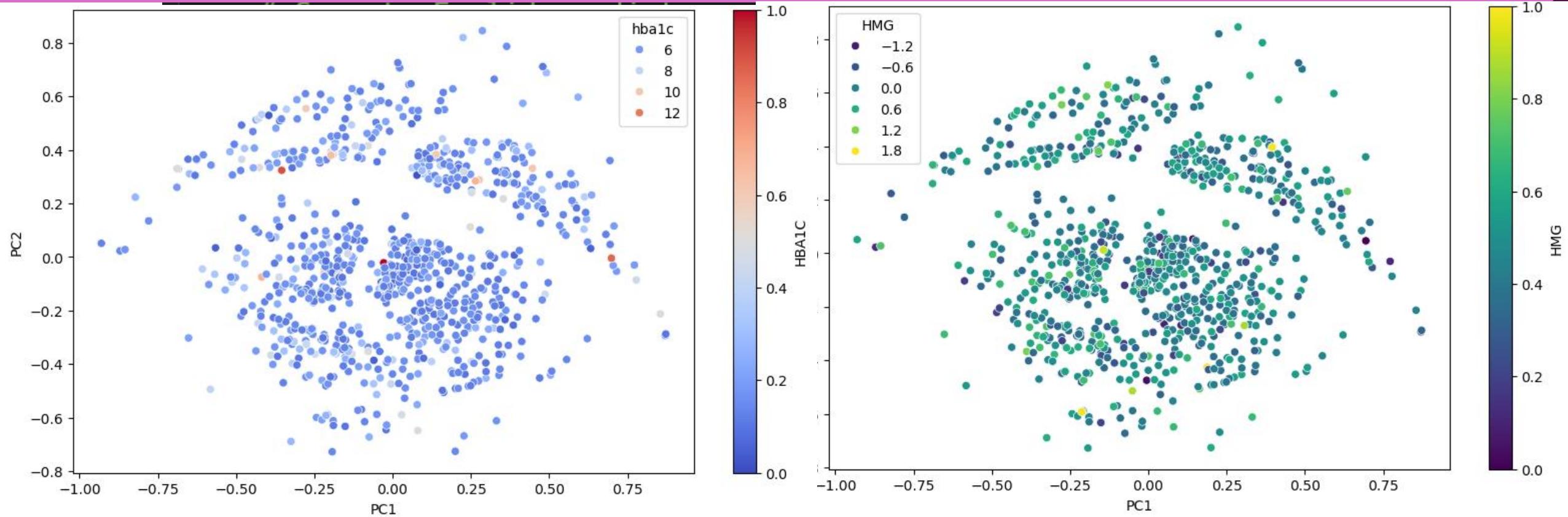


- Should we let the data make the categories for us
- Should we use what we know: processed vs non, veggie vs carnivore
- What are the other things at play here

Background

Methods

Results



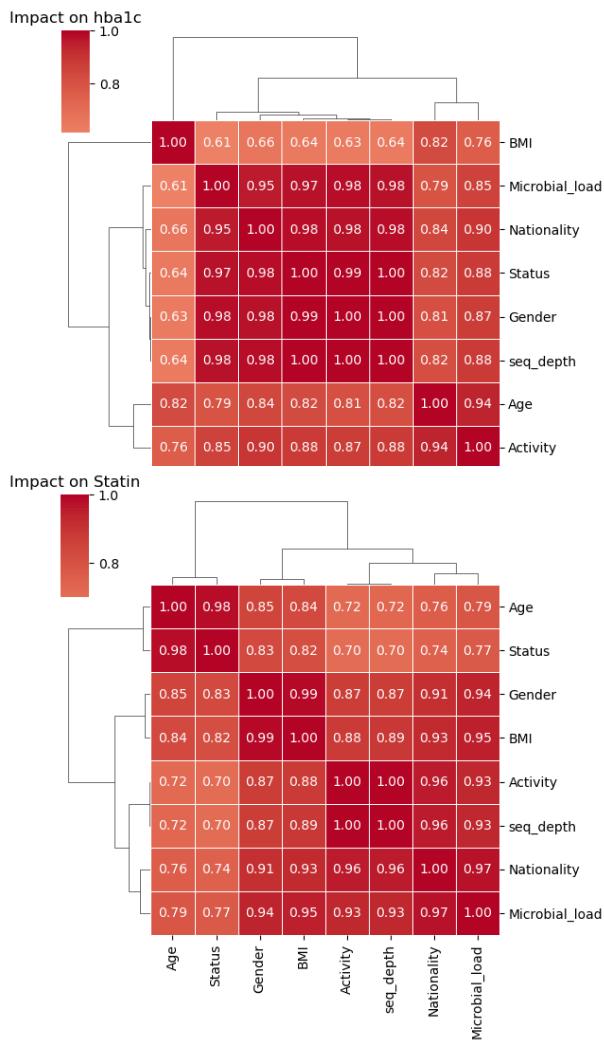
Mantel test between Bray-Curtis and HMG: $r=0.0274$, p-value=0.1230

Mantel test between Bray-Curtis and HBA1C: $r=0.0604$, p-value=0.0020

Mantel test (Statin=1) between Bray-Curtis and HMG: $r=0.0047$, p-value=0.8800

Mantel test (Statin=1) between Bray-Curtis and HBA1C: $r=0.0109$, p-value=0.7330

Linear Regressions



Chicken

Peanuts

Hibiscus

Hibiscus

Wild Boars

Pig

Apple

Apple

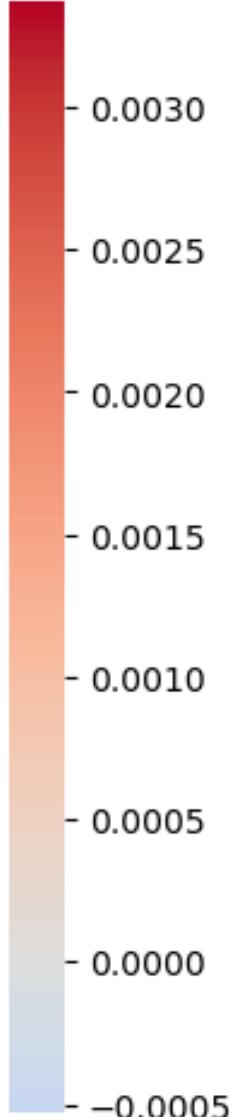
Walnut

Cattle

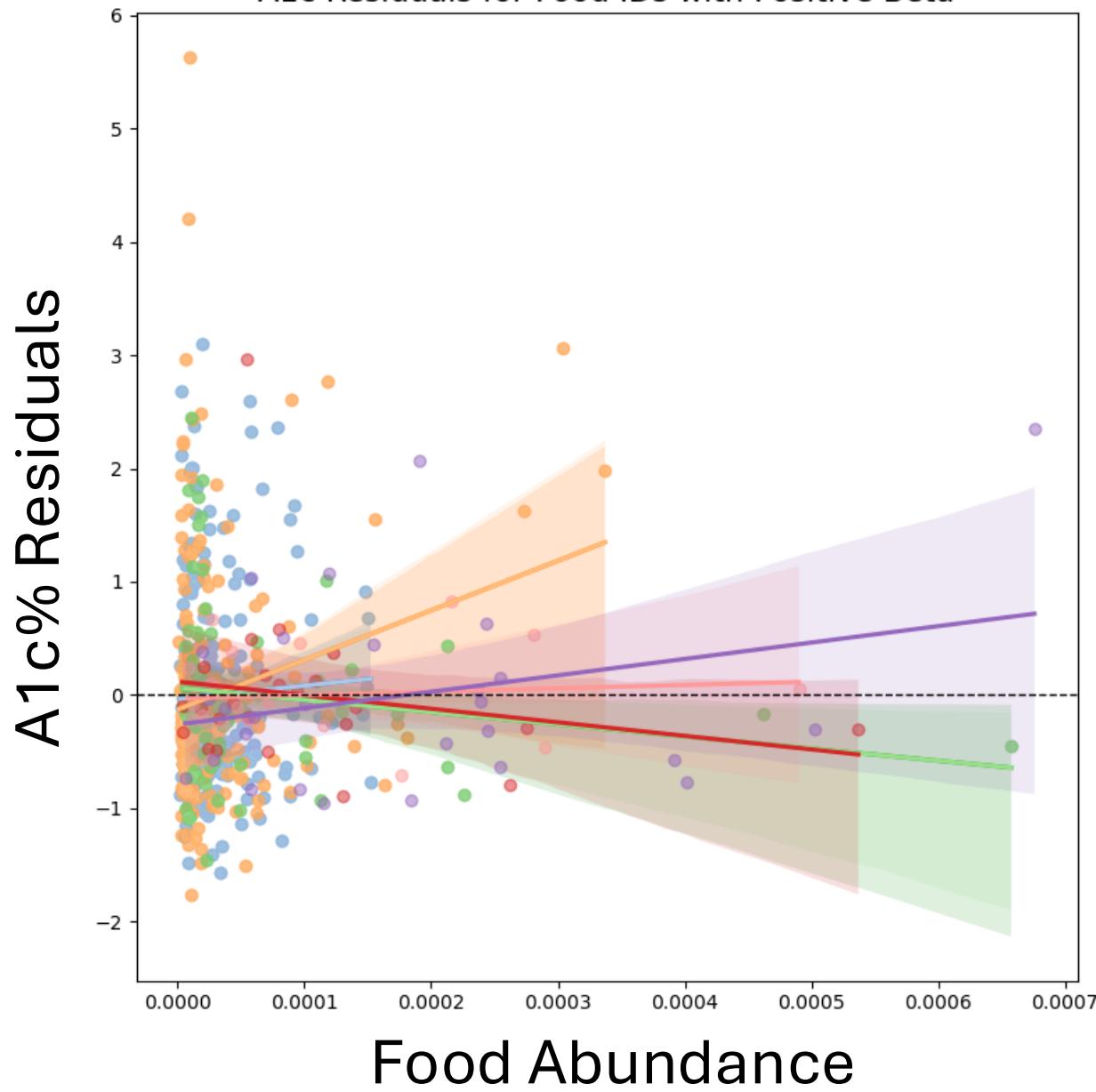
Sesame

A1c ~ load + Age + Nationality + HMG*Diet

Independent Features (Diet)	Beta (diet)	Beta (Interaction HMG * Diet)
	Beta Values	
food_id_334	-0.00034	-0.00053
food_id_16	-0.00017	-0.00051
food_id_457	0.00003	-0.00002
food_id_748	0.00003	-0.00002
food_id_310	0.00003	-0.00003
food_id_549	0.00003	-0.00003
food_id_105	0.00072	0.00026
food_id_348	0.00072	0.00026
food_id_94	0.00136	0.00042
food_id_506	0.00158	0.00006
food_id_170	0.00337	0.00082



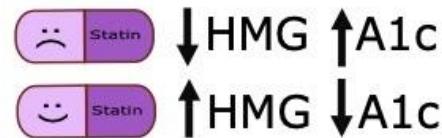
A1c Residuals for Food IDs with Positive Beta

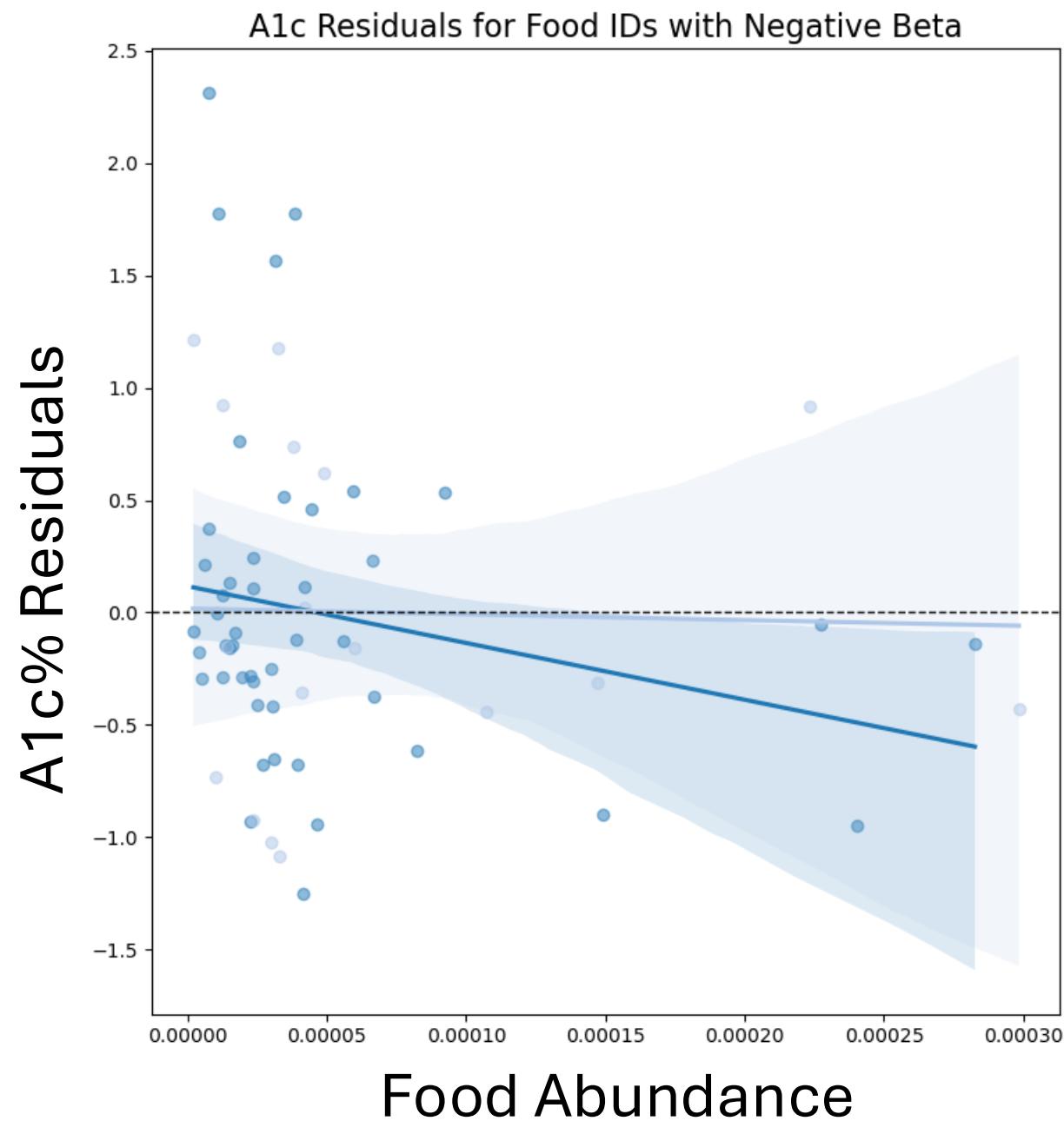


Food ID (Beta)

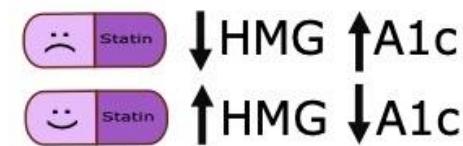
- food_id_457 (Beta: 0.0000)
 - food_id_748 (Beta: 0.0000)
 - food_id_310 (Beta: 0.0000)
 - food_id_549 (Beta: 0.0000)
 - food_id_105 (Beta: 0.0007)
 - food_id_348 (Beta: 0.0007)
 - food_id_94 (Beta: 0.0014)
 - food_id_506 (Beta: 0.0016)
 - food_id_170 (Beta: 0.0034)

Hibiscus
Hibiscus
Wild Boar
Pig
Apple
Apple
Walnut
Cattle
Sesame





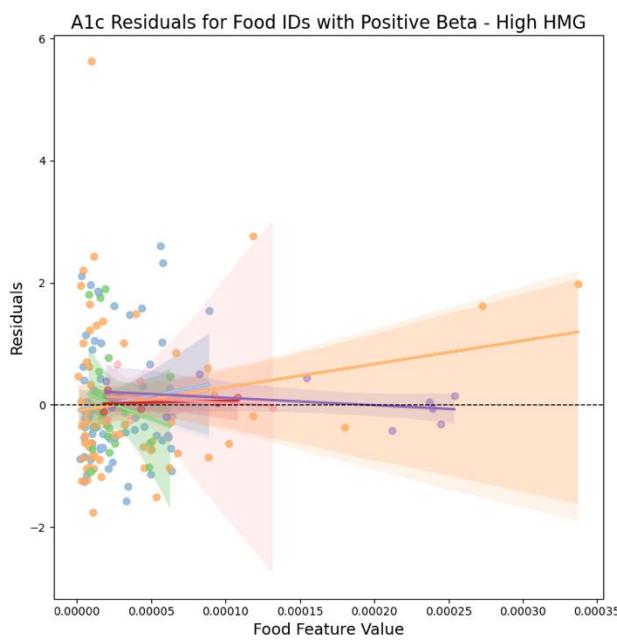
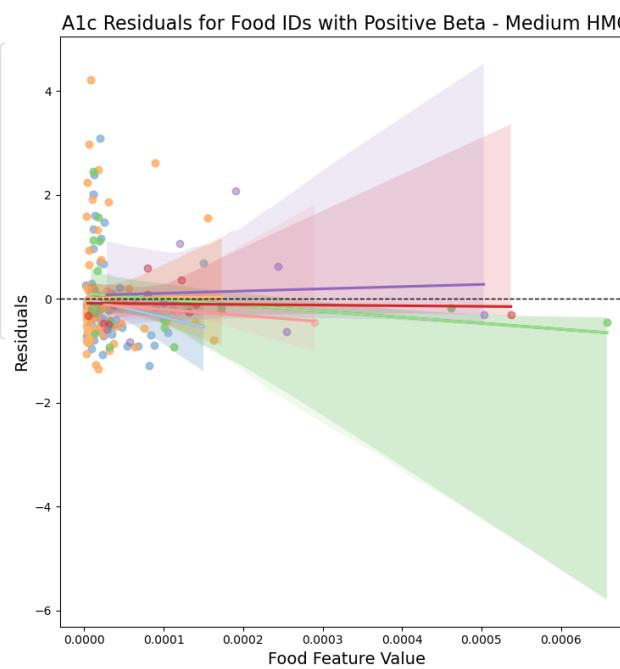
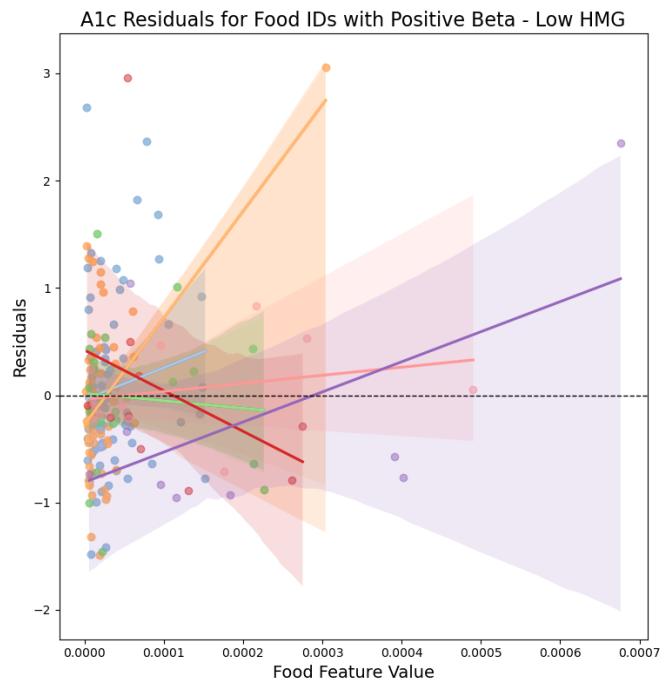
Chicken
Peanuts



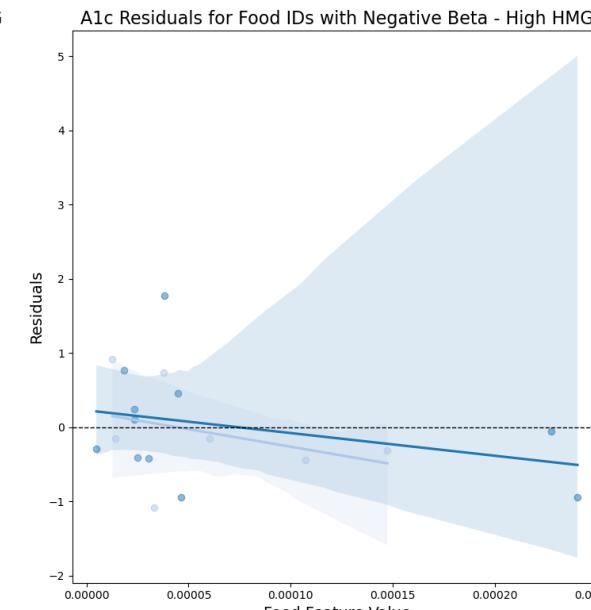
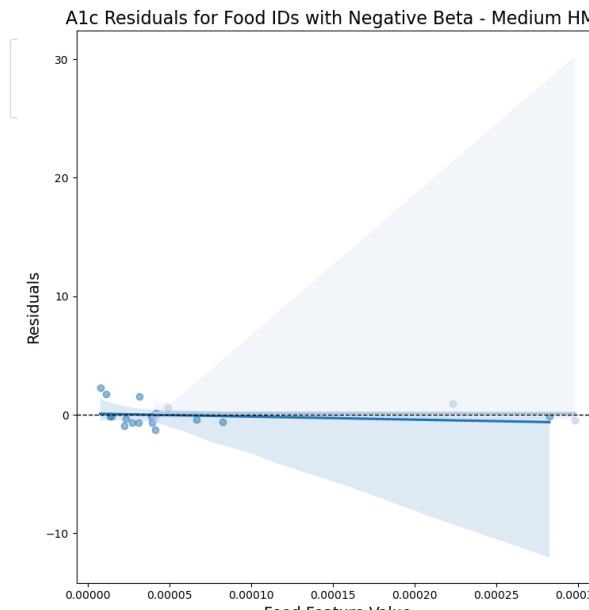
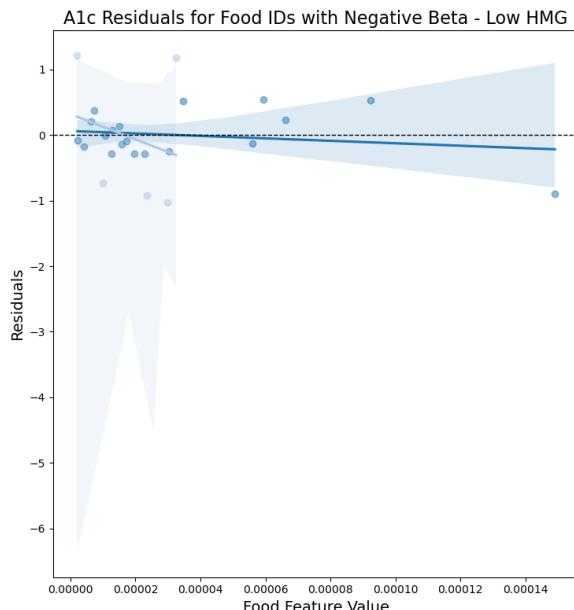
Background

Methods

Results



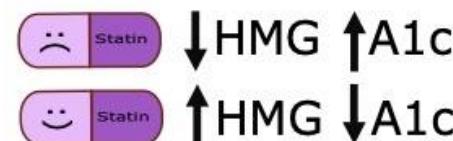
- Hibiscus
- Hibiscus
- Wild Boar
- Pig
- Apple
- Apple
- Walnut
- Cattle
- Sesame



Food ID (Beta)

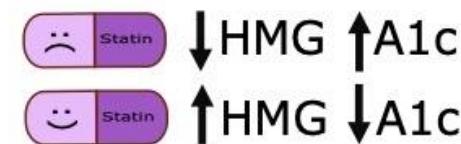
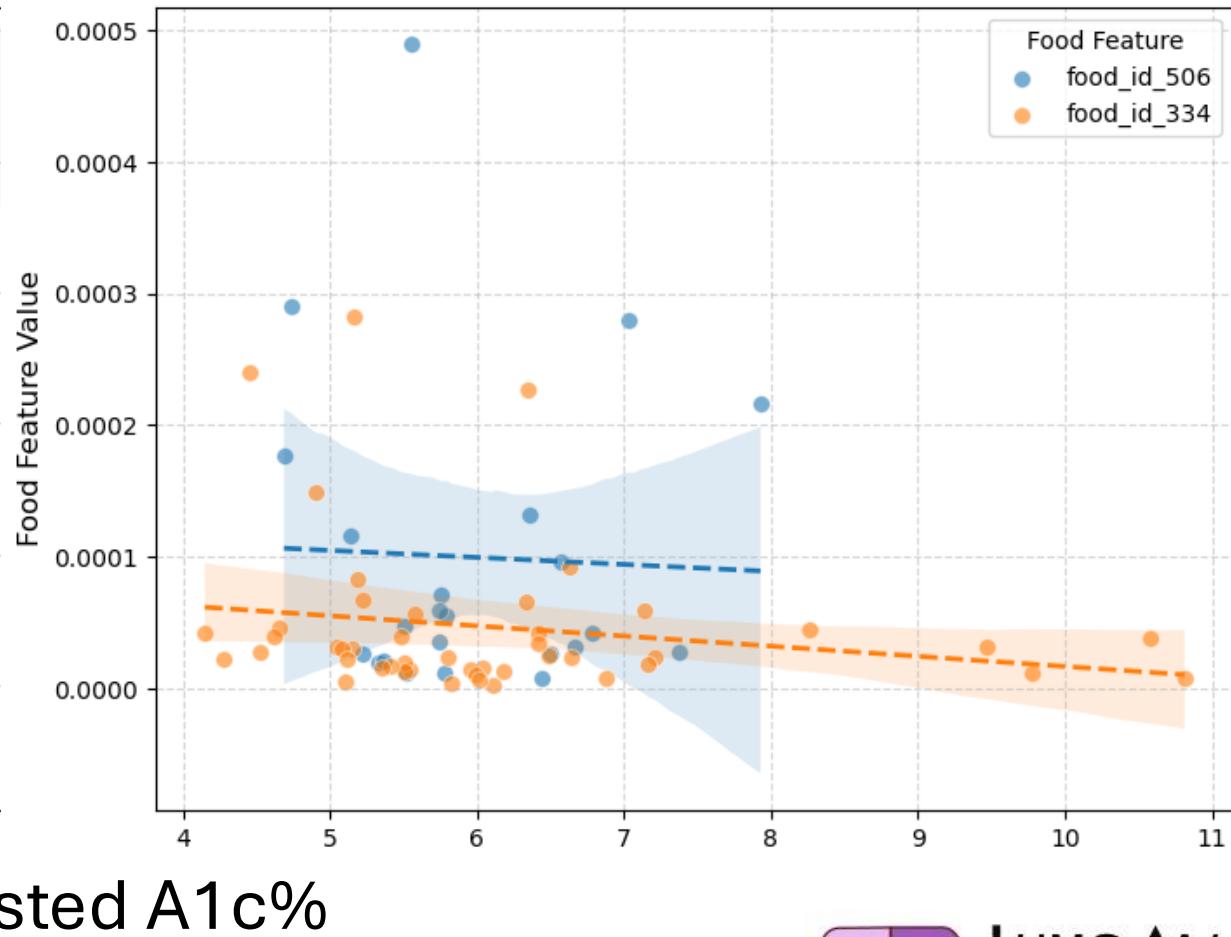
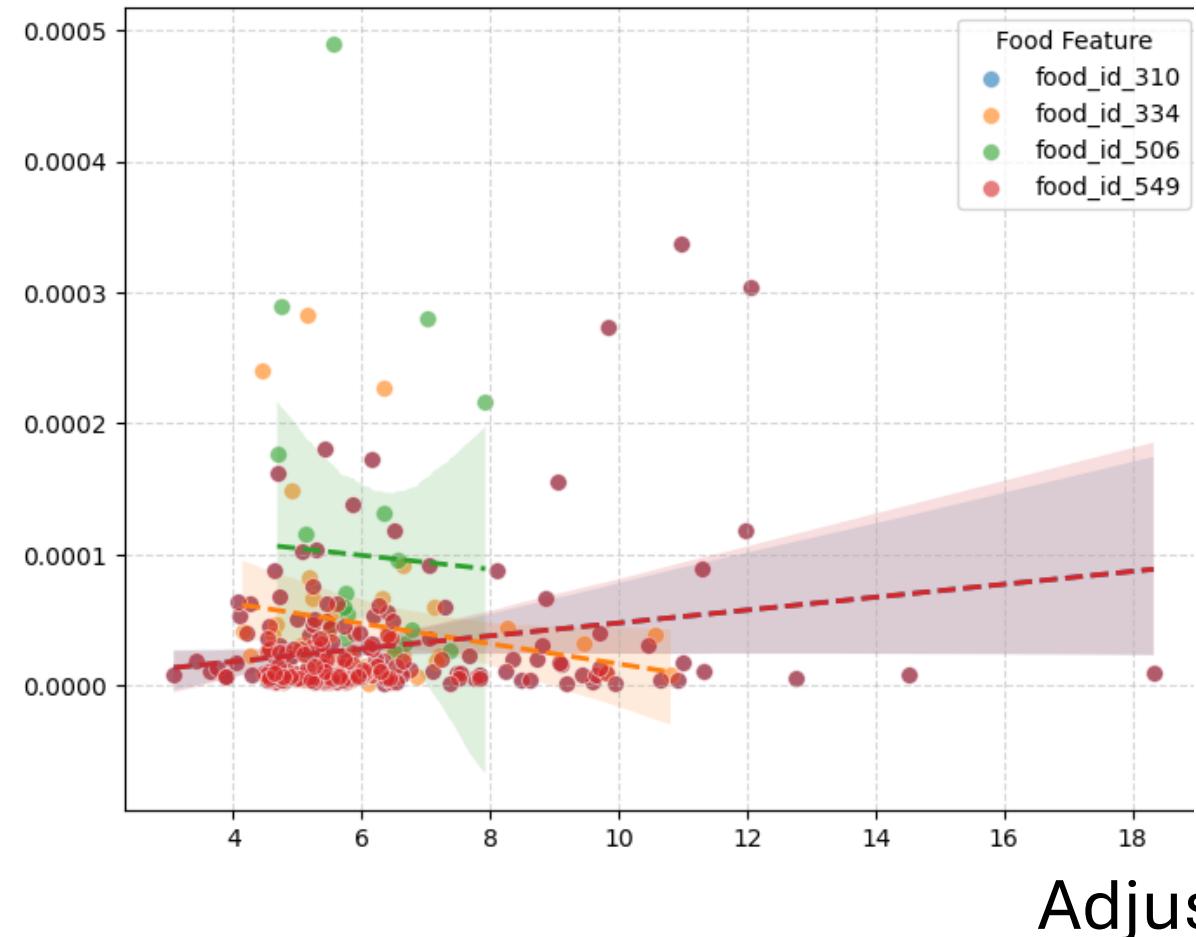
- food_id_334 (Beta: -0.0003)
- food_id_16 (Beta: -0.0002)

Chicken
Peanuts

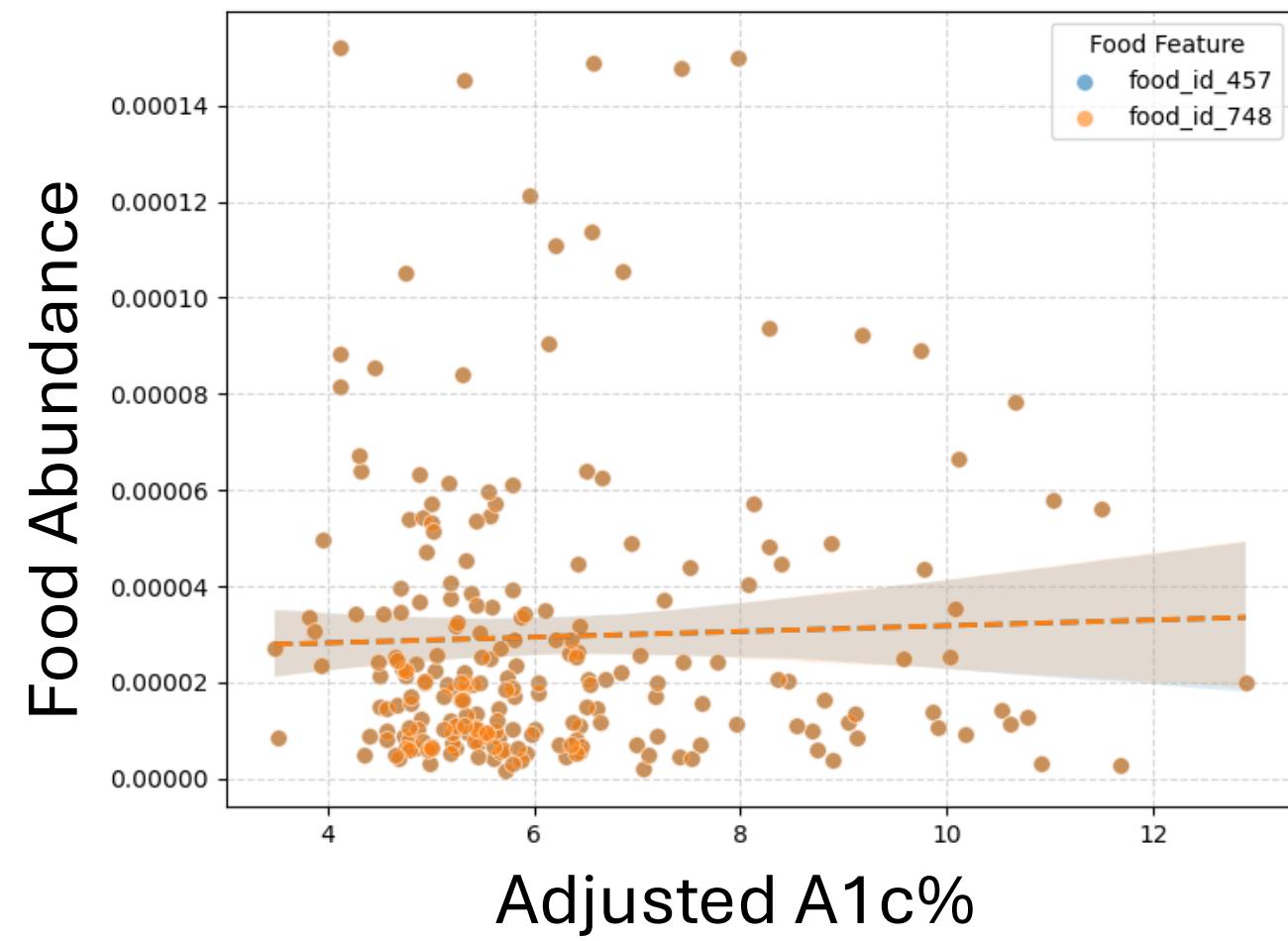
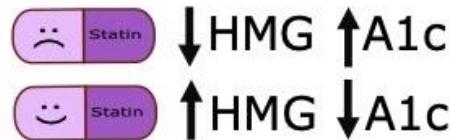


Meat, take out swine your left with cattle and chicken

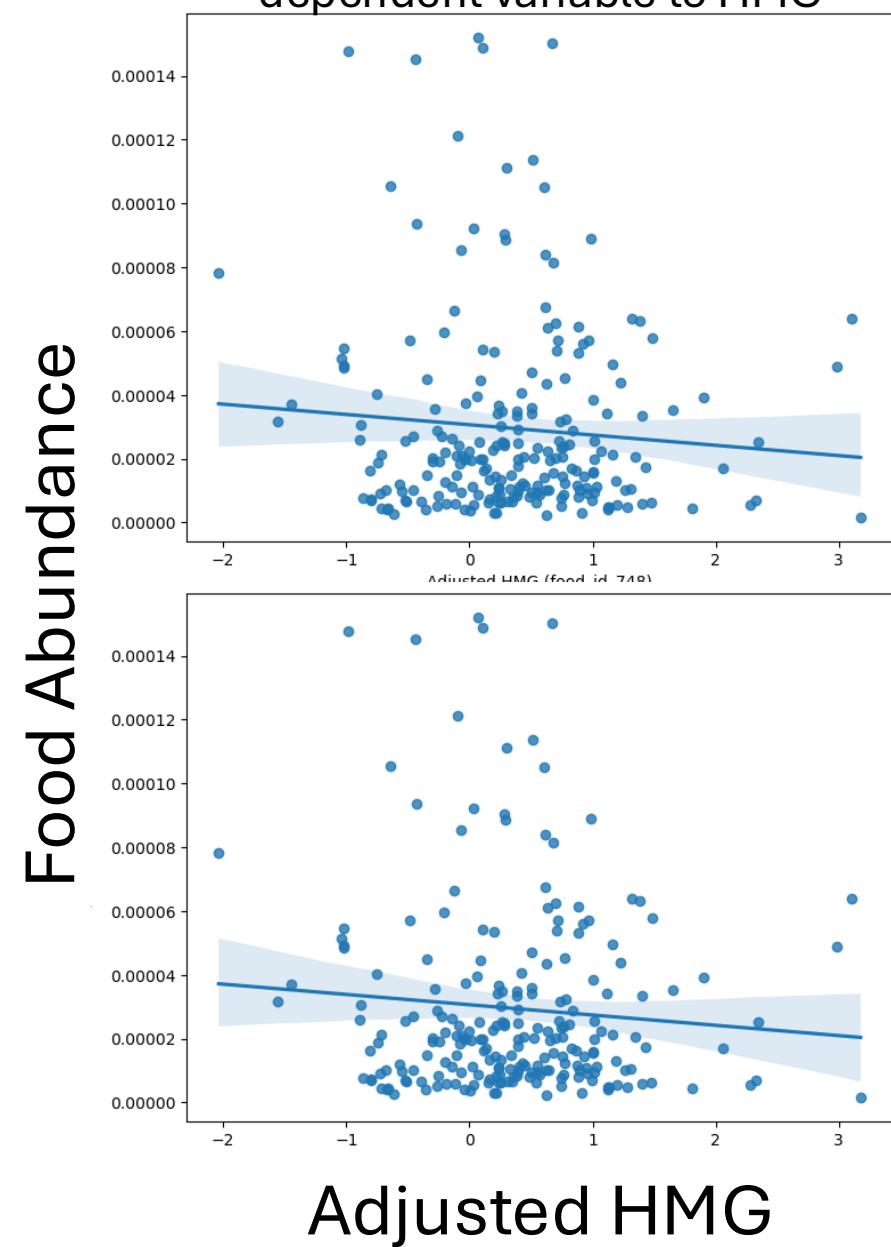
Food Abundance



Hibiscus /Cotton DNA

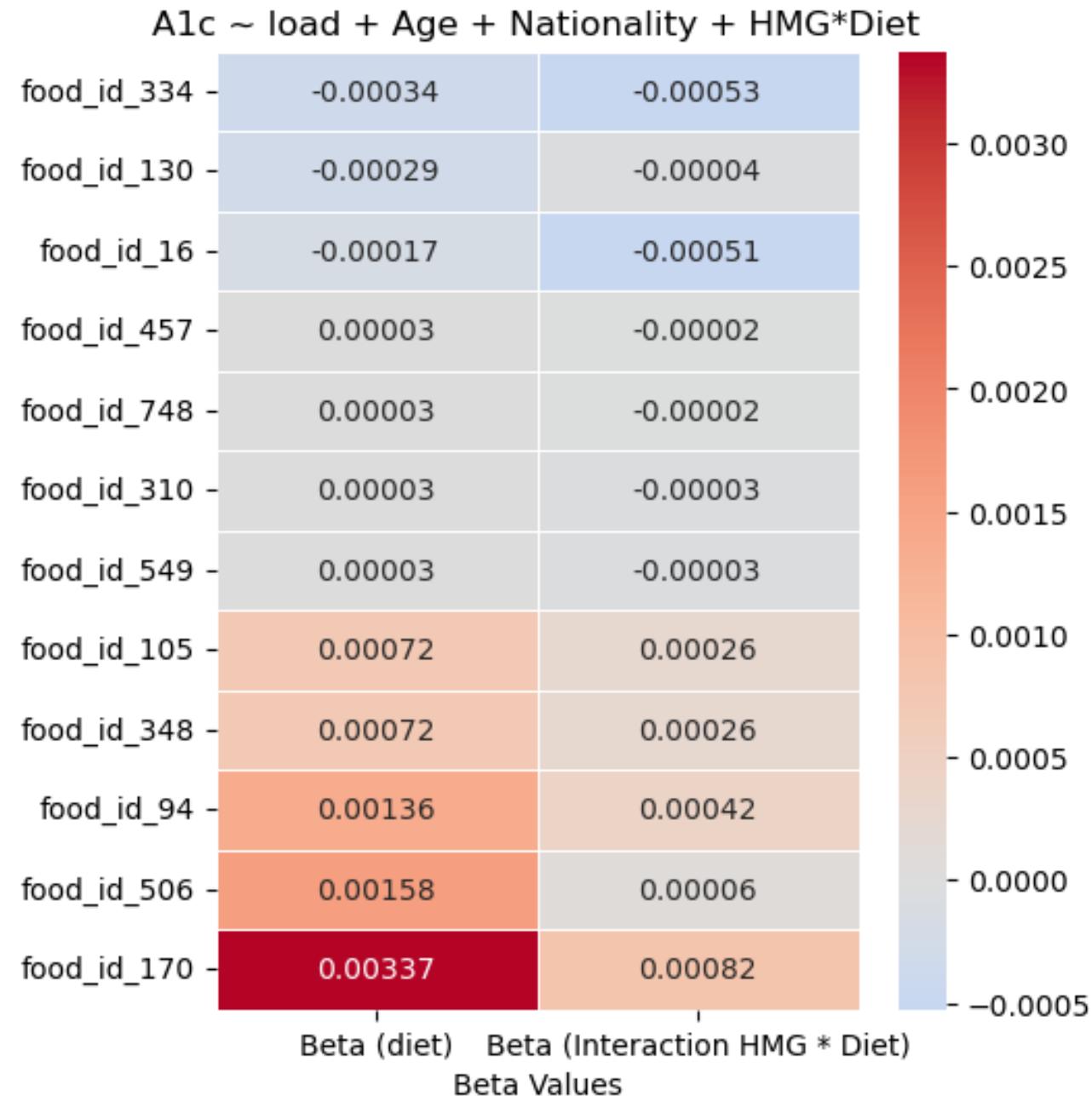
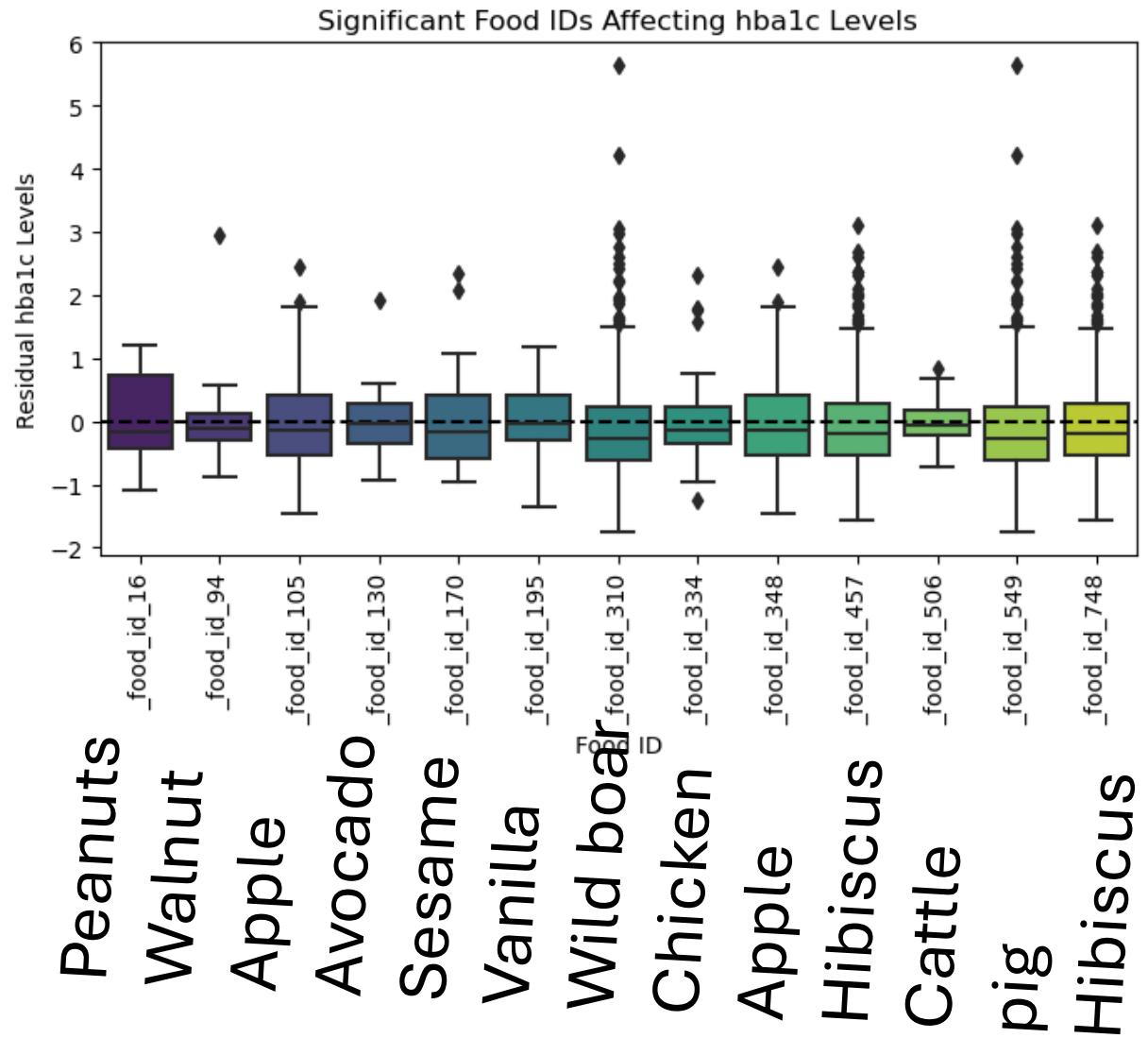


The only significant when switch dependent variable to HMG

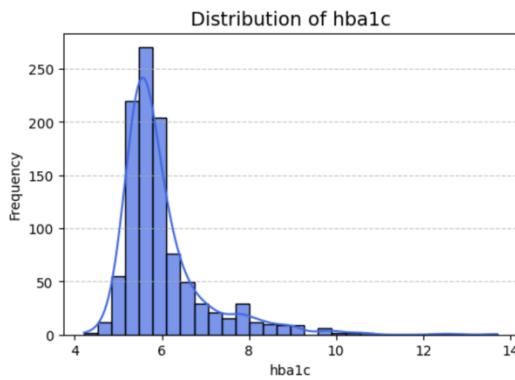


Linear Regression

for $q < 0.1$



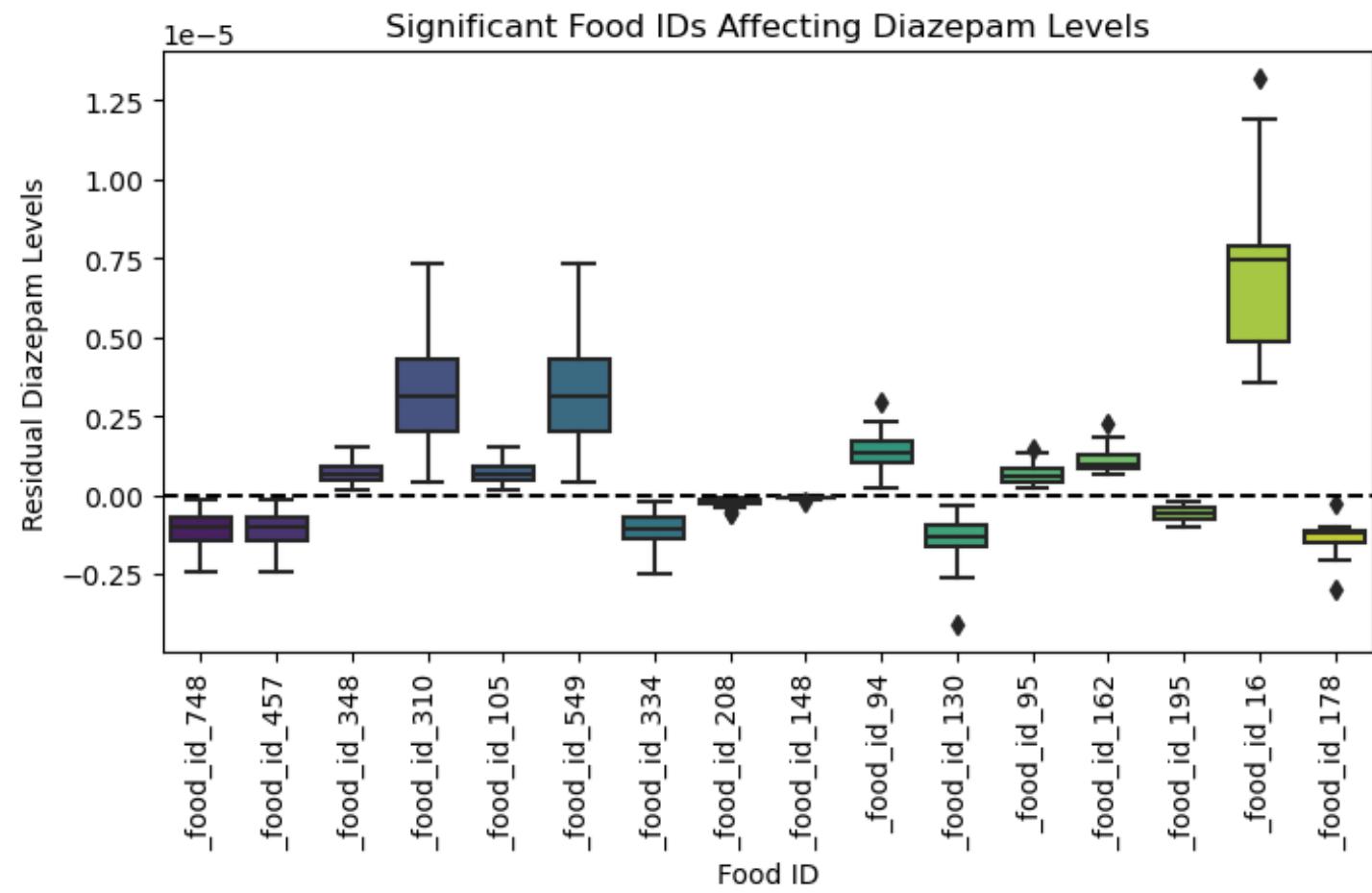
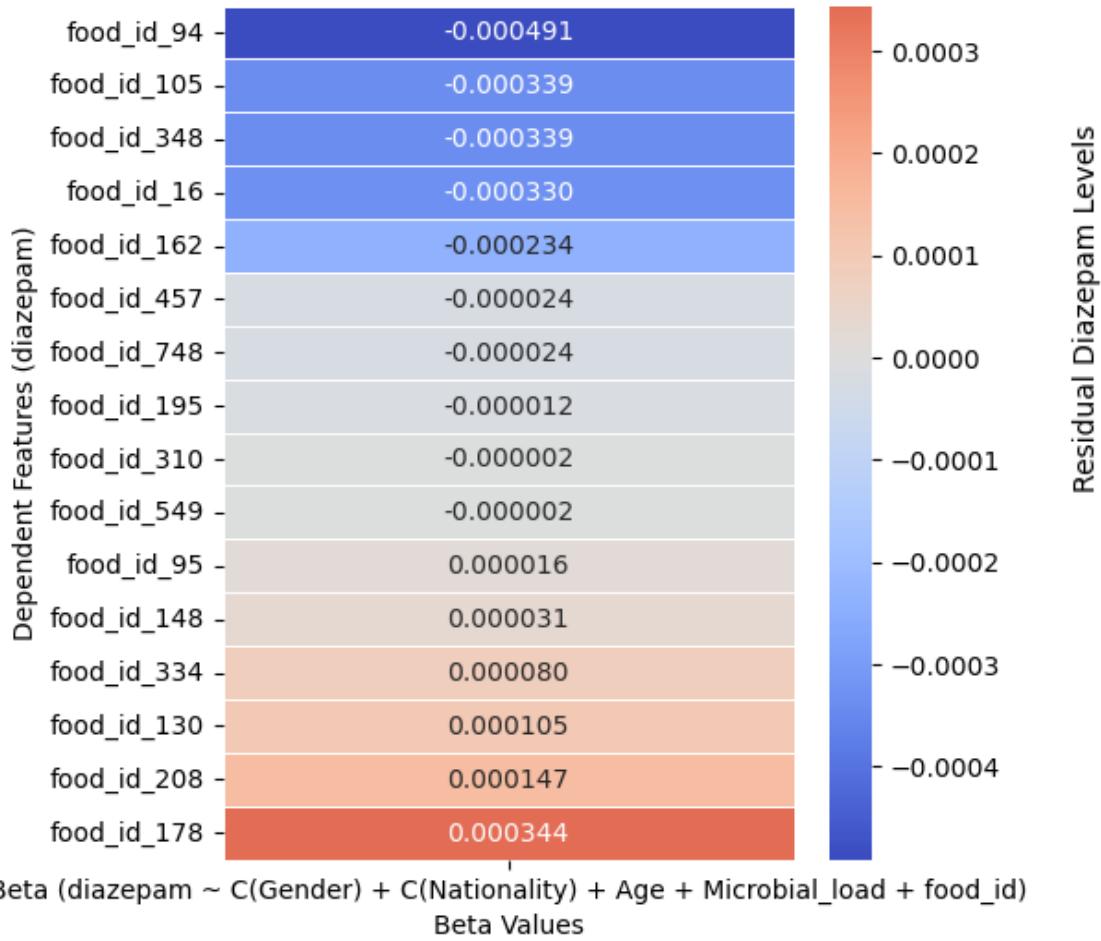
What the Dietitian had to say



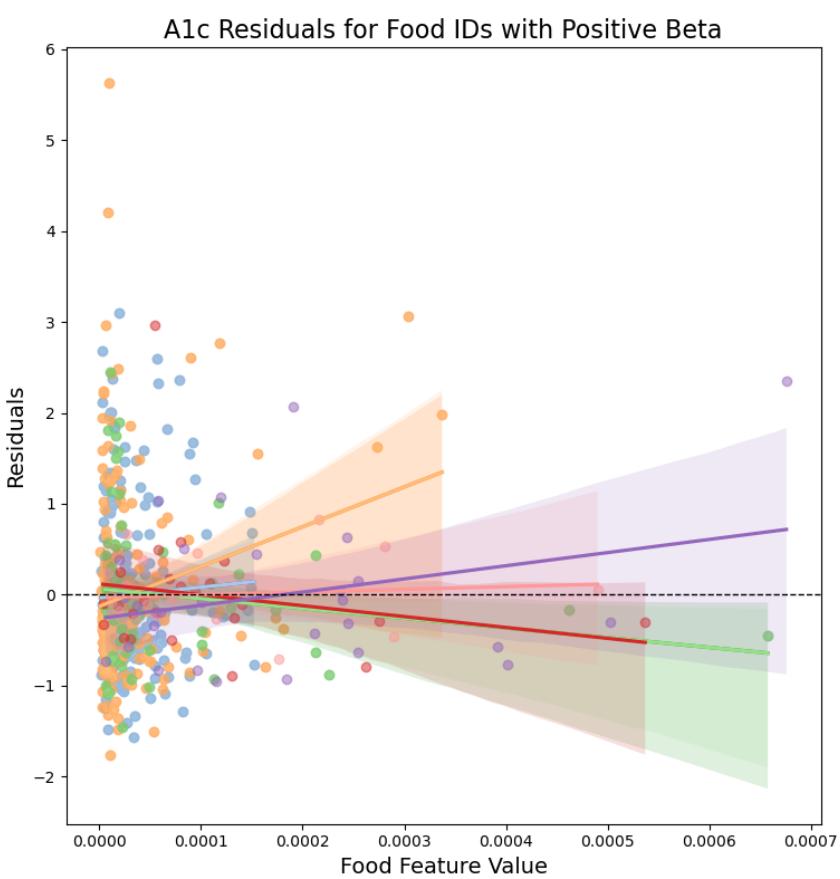
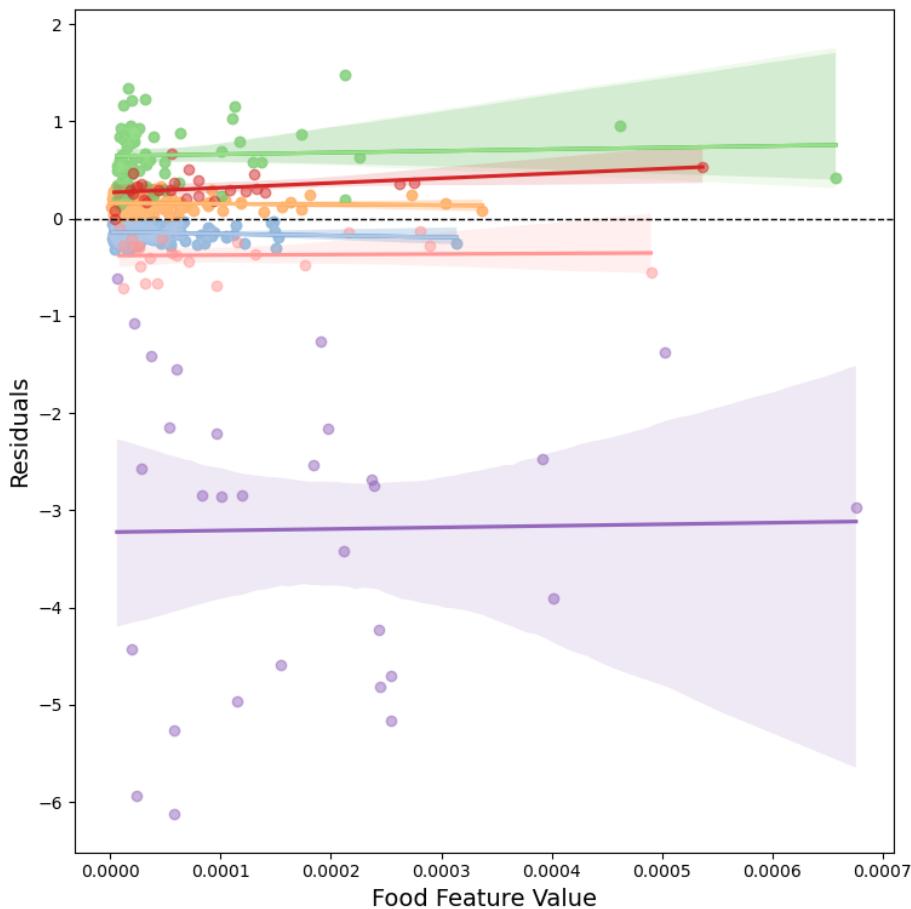
- A1c is also a marker for how well your blood sugar is stabilized so if it's high that means your blood sugar has been high more often
- When you have diabetes you're supposed to keep A1c level (under 9%) your brain has to work hard when you have high A1c
- Just eating straight carbs will go straight through your body so you're advised to eat them with protein or fat to help them stay in your stomach longer (chicken and nuts make sense apples not so much)
- She also recommended looking at the USDA/FDA fraud list cause spices and wine are often caught and could explain some of the hibiscus
- Also Pork/Swine being any part of the pig beef sticks etc. a weird thing that isn't regulated

$$\text{Beta (diazepam} \sim \text{C(Gender)} + \text{C(Nationality)} + \text{Age} + \text{Microbial_load} + \text{food_id})$$

Diazepam



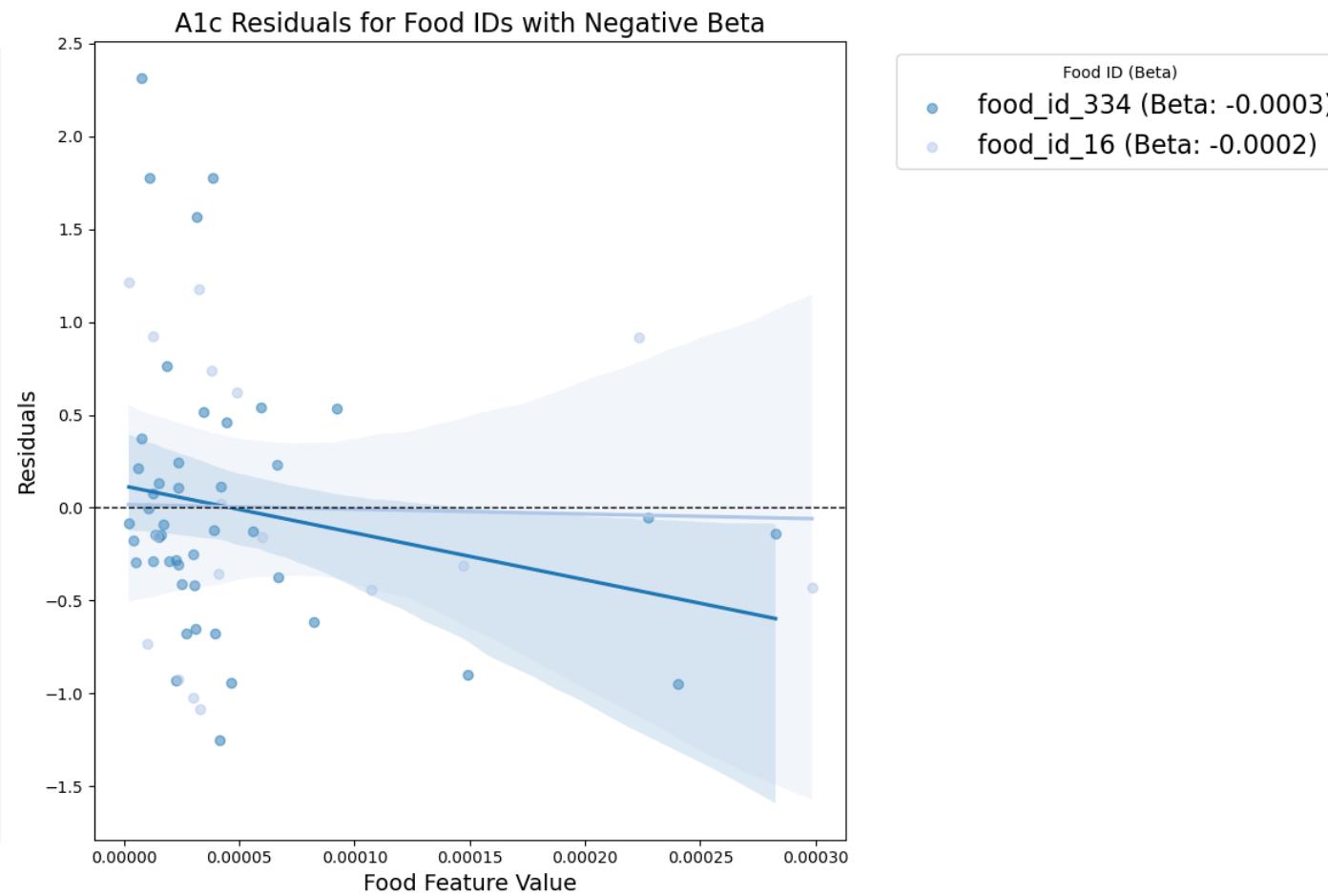
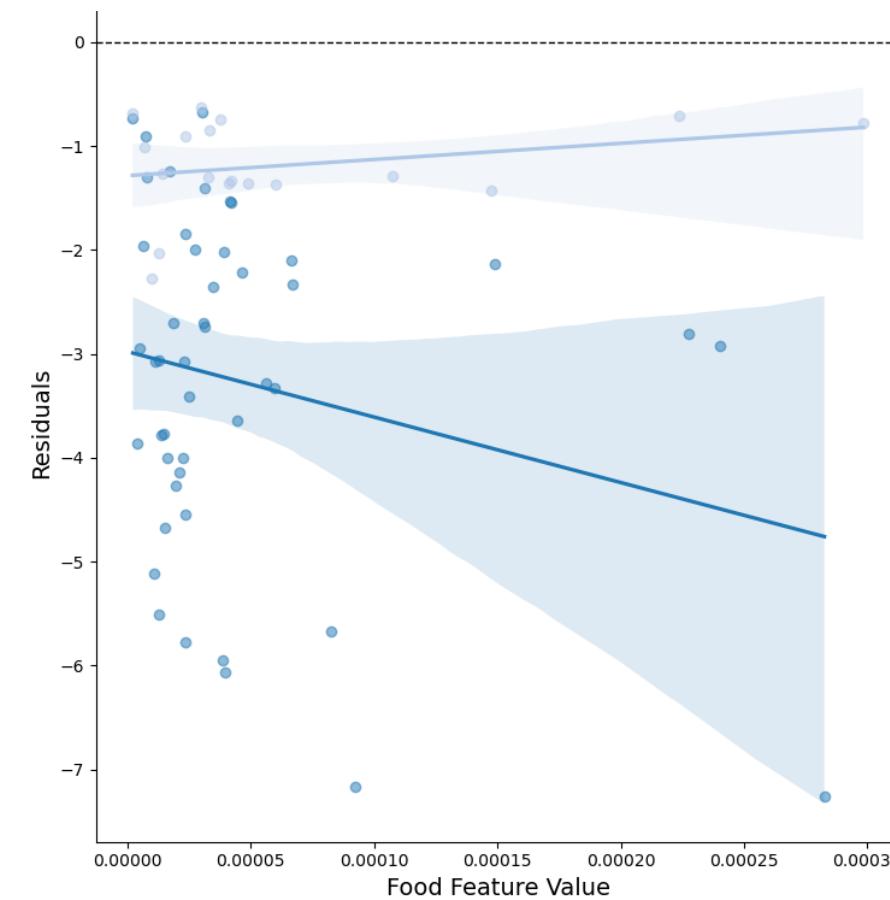
Diazepam



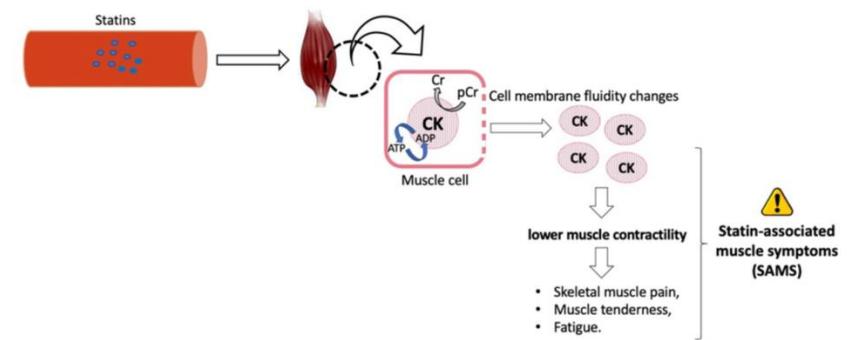
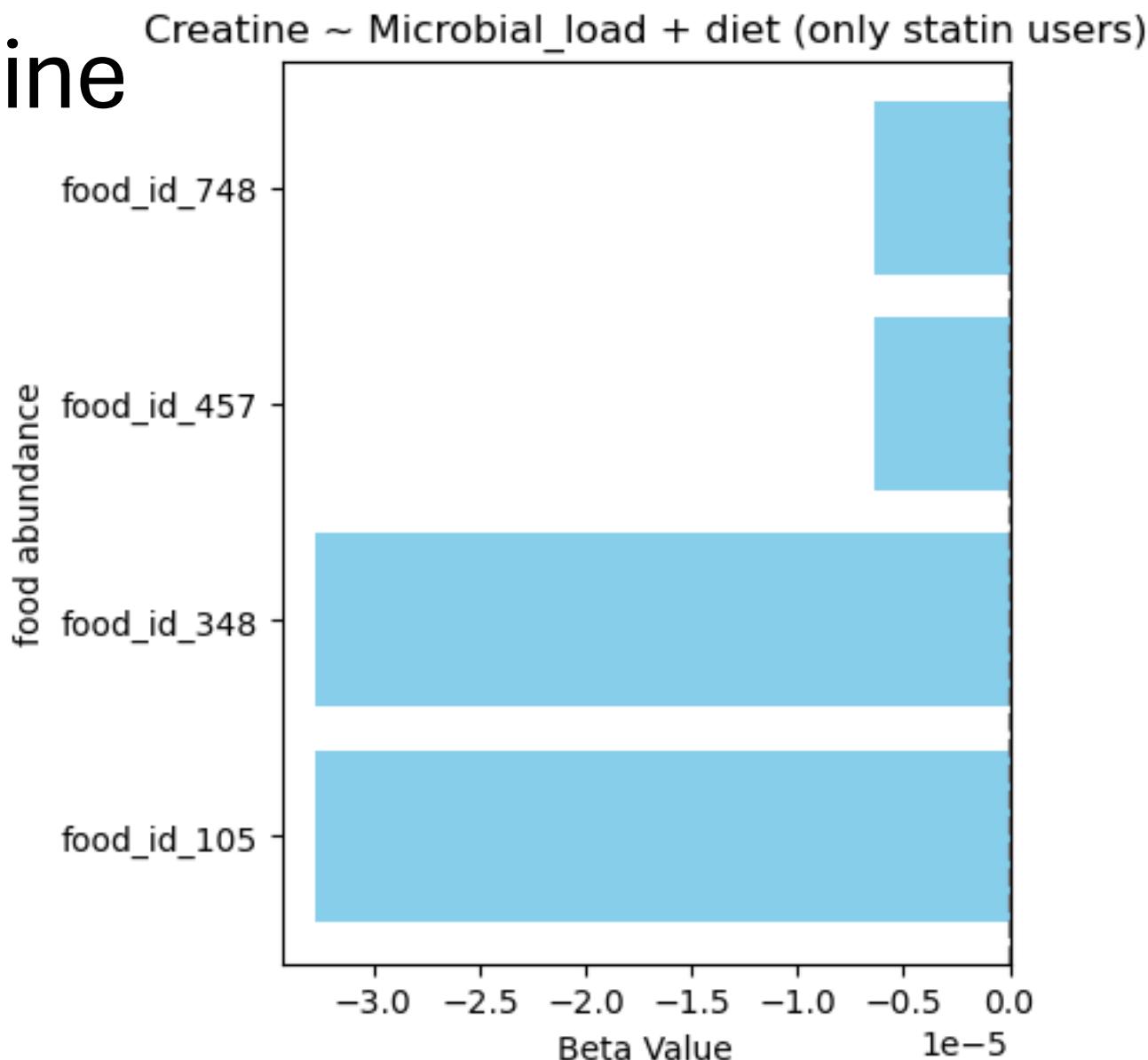
Food ID (Beta)
food_id_457 (Beta: 0.0000)
food_id_748 (Beta: 0.0000)
food_id_310 (Beta: 0.0000)
food_id_549 (Beta: 0.0000)
food_id_105 (Beta: 0.0007)
food_id_348 (Beta: 0.0007)
food_id_94 (Beta: 0.0014)
food_id_506 (Beta: 0.0016)
food_id_170 (Beta: 0.0034)

Beta (diazepam ~ C(Gender) + C(Nationality) + Age + Microbial_load + food_id)

Diazepam



Creatine



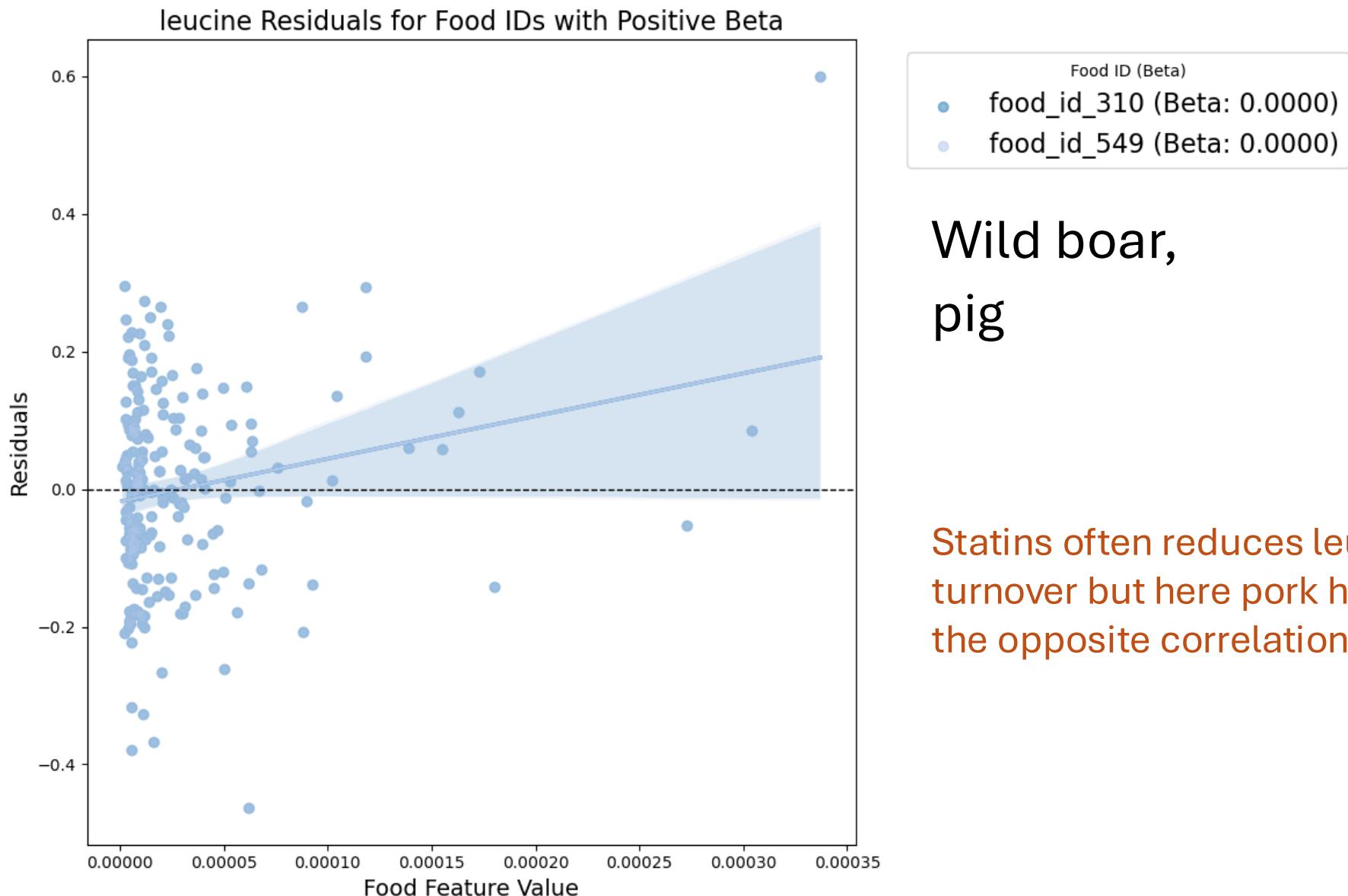
High protein diets would lead to high creatine

348 = Malus(apple)
105 = Apple

So maybe high fruit veg diets are giving negative correlation

Statin users probably want higher creatine for less severe side effects

leucine



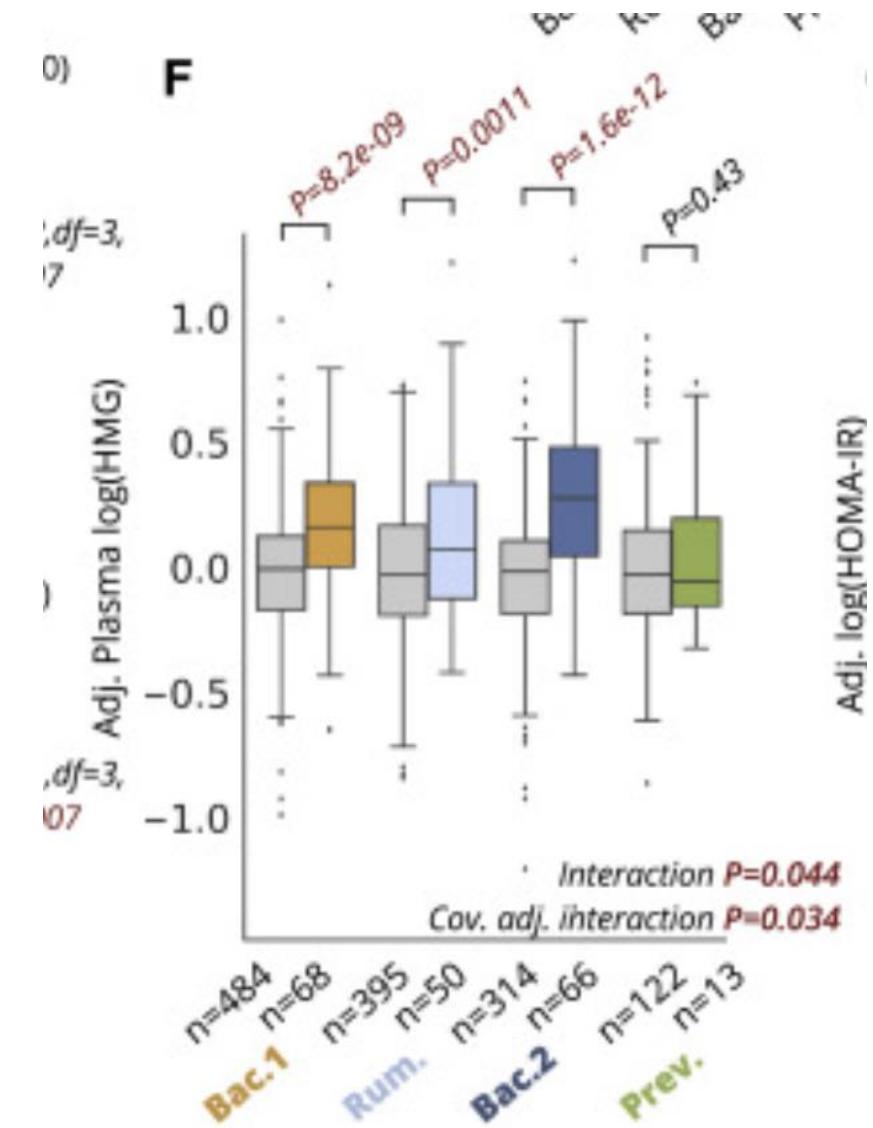
Wild boar,
pig

Statins often reduces leucine turnover but here pork has the opposite correlation

Linear Regressions: Microbes

Was having a hard time replicating studies which proved relationship with certain microbes and HMG or A1c using the model:

HMG or A1c ~ CoVars + Microbe:Statin



Linear Regressions: Microbes

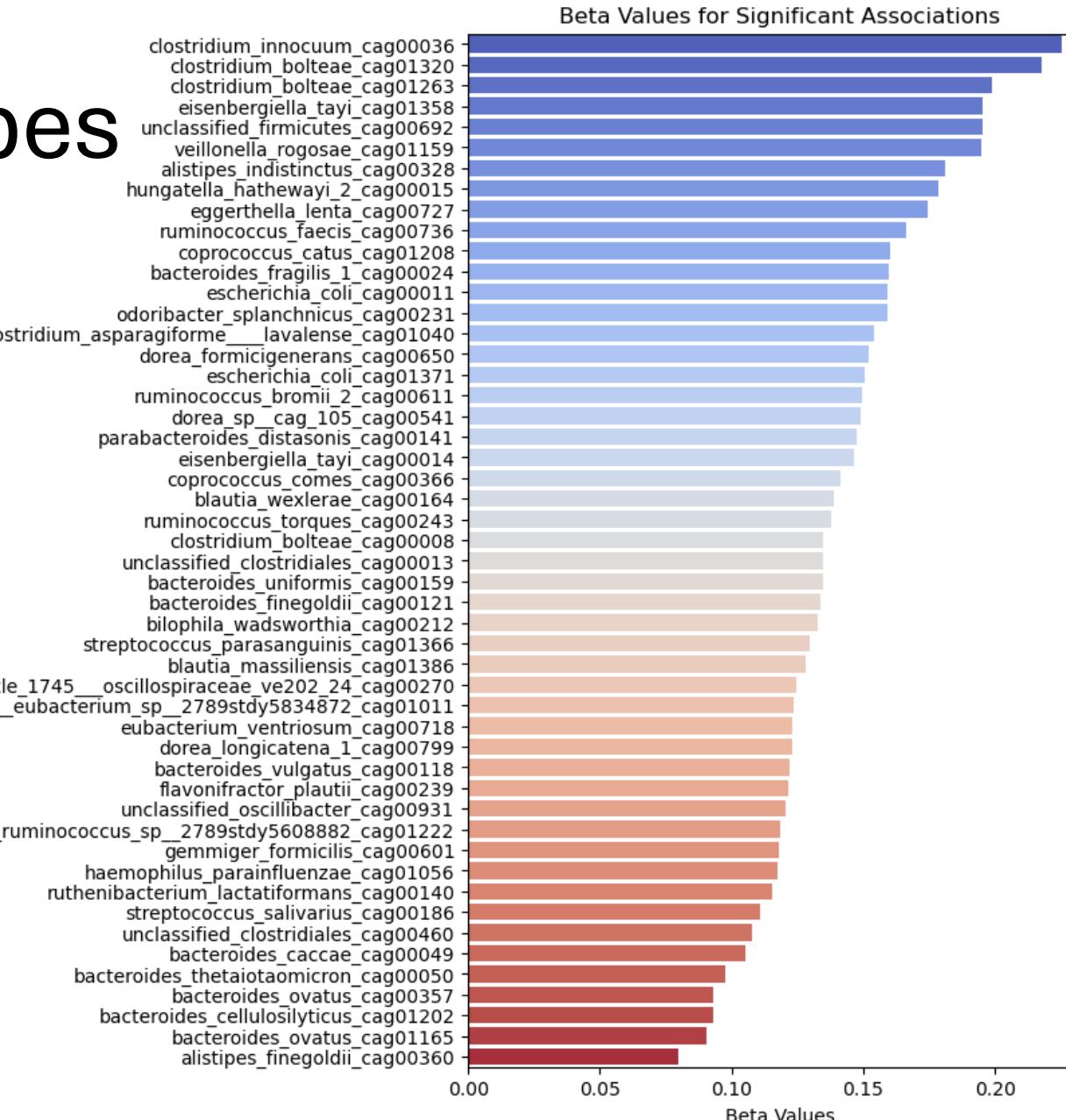
$\text{microbe} \sim \text{seq_depth} + \text{Age} + \text{Activity} + \text{HMG}^*\text{A1c}$

only in statin users

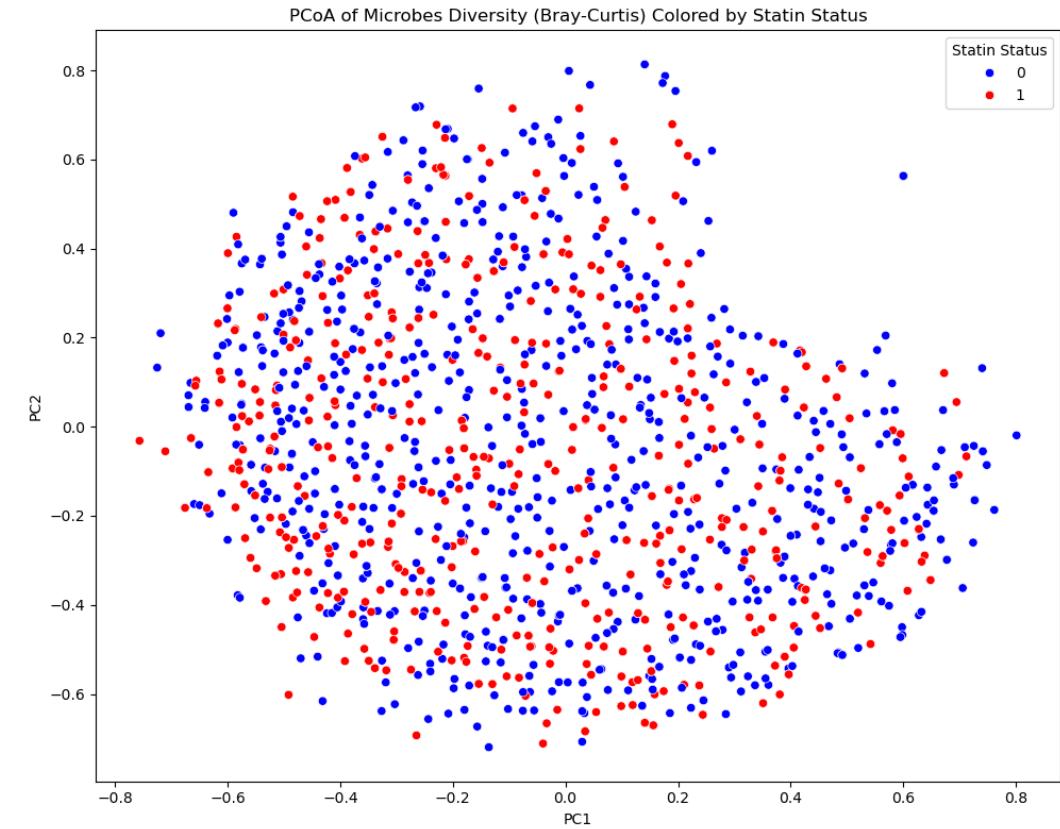
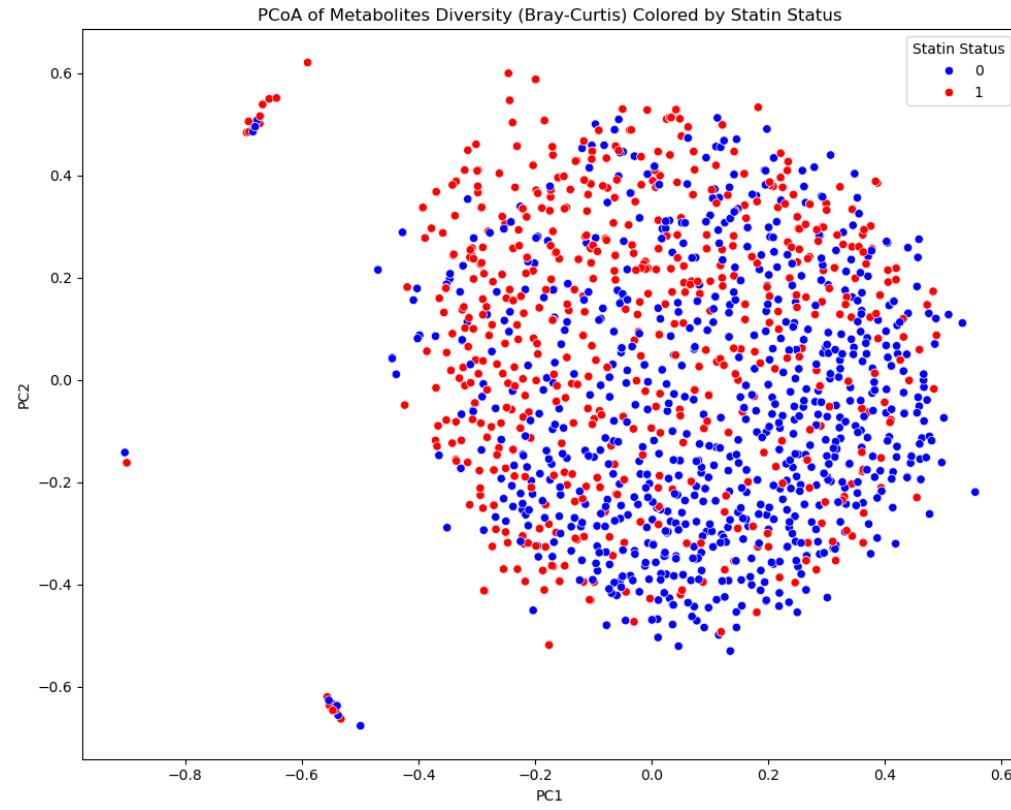
Independent Features (Microbes)

oscillibacter_sp_kle_1728_kle_1745_oscillospiraceae_ve202_24_cag00270
ruminococcus_sp_2789stdy5608817_eubacterium_sp_2789stdy5834872_cag01011

blautia_sp_marseille_p3087_ruminococcus_sp_2789stdy5608882_cag01222



PCoA plots of microbe beta diversity and metabolite beta diversity colored by statin use



Key Take Aways

- Covariates: BMI and Status are confounding with statins, since microbial load is important for diet regressions maybe confirms mediation
- Maybe there's a way to group people by diet to make better analysis. As MED1 improves it's probably worth it to try some of these analysis again
- A1c continues to be a good biomarker to analyze statins
- Lots of things to think about for analyzing interaction of diet on medications

Future Directions

- Mediation!
- Look at some of the other metabolites (ALT/AST weren't found in the meta cardis I was looking at but maybe they're out there)
- Medi vs Metabolome (maybe you'll see diet is less important for cholesterol when on statins)
- Mental on Medi vs Metabolome and Medi vs Microbes
- Can we apply this to other medications? What would be a general strategy to find Diet \leftrightarrow Meds interactions
- ML idea: pre classify people as responders vs non responders who are on statins
 - Then see if diet profile could predict

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