*Food Forum*
*Dietary Patterns and Diet-Related Chronic Diseases Across the Lifespan*
*August 15-16, 2023*

# Beyond Traditional Nutrition Markers for Assessing Dietary Quality and Chronic Disease Risk

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Fred Hutchinson Cancer Center

# Disclosures

| AFFILIATION/FINANCIAL INTERESTS (prior 12 months) | ENTITIES |
|---|---|
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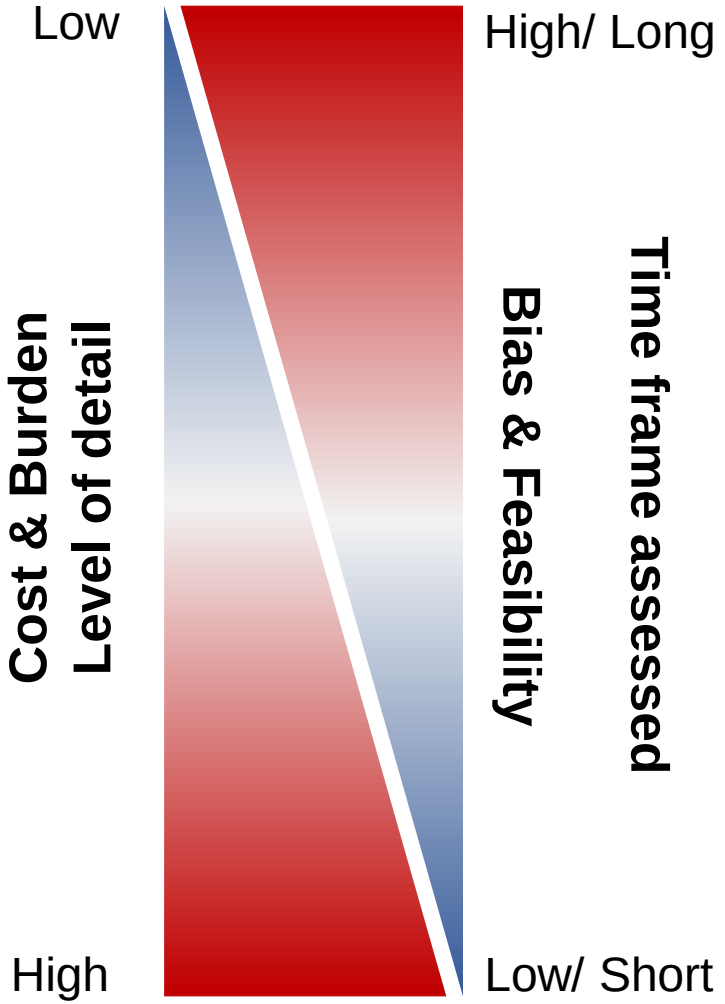
# The human diet is a complex exposure

- 1000s of compounds
  - Nutrients
  - Phytochemicals
  - Other bioactives
  - Contaminants
- Complex mixtures
  - Foods
  - Classes of foods
  - Food groups
  - Dietary patterns

# Differences in ways to assess diet




Screeners
- Online
- Paper/pencil

Food frequency questionnaire (FFQ)
- Online
- Paper/pencil

24hr diet recall
- Automated
- In person

Multiple days

Food records
- Unweighed
- Weighed

Multiple days

Direct observation

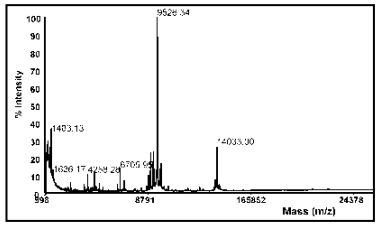
Provided diets
- Chemical analysis

**Evolving technologies**

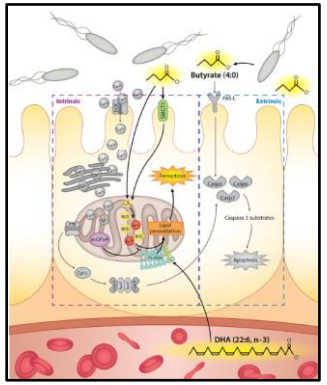
Electronic recording
Photography
Sensors
Biomarkers

https://dietassessmentprimer.cancer.gov/

# Application of Dietary Biomarkers



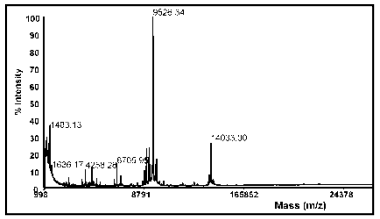




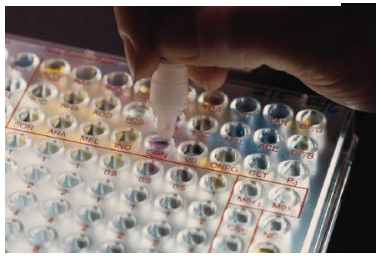

- Provide objective evaluation of exposure to nutrients, dietary constituents, foods, food groups, or dietary patterns.
- Validate dietary assessment instruments or self-reported dietary data.
- Calibrate dietary intake data collected using self-report and known to have biases.
- Establish a biological link between a dietary factor and  physiological or biochemical process.

# Omics Biomarkers in Dietary Assessment

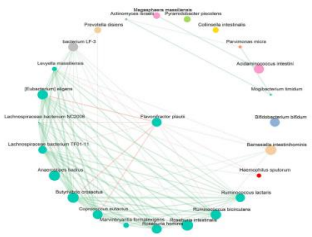
Metabolomics




Proteomics



Gut microbiome

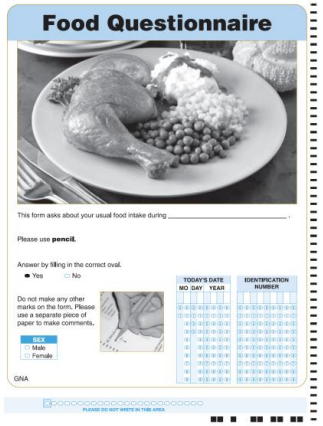


## Simultaneous analysis of multiple measures in biospecimens

- **Metabolome**:  metabolites in blood, urine, tissue
- **Proteome**: proteins in blood, urine, tissue
- **Microbiome**:  microbial measures in stool, gut luminal contents, tissue
  - 16S rRNA gene (taxanomic classification)
  - Metagenome (functional capacity)
  - Metatranscriptome (gene expression)

# Observational Studies of Biomarkers of Dietary Patterns and Diet Quality

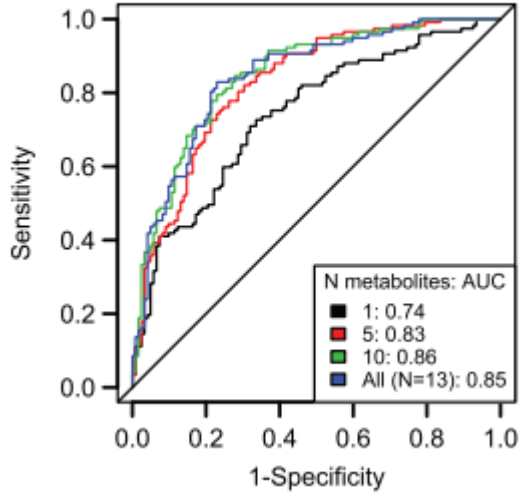
- Cross-sectional studies have identified various collections of candidate biomarkers associated with consumption of high- vs low-quality diets




**Calculation of diet quality scores from self-reported diet**

+

**Analysis of biospecimen for biomarkers**



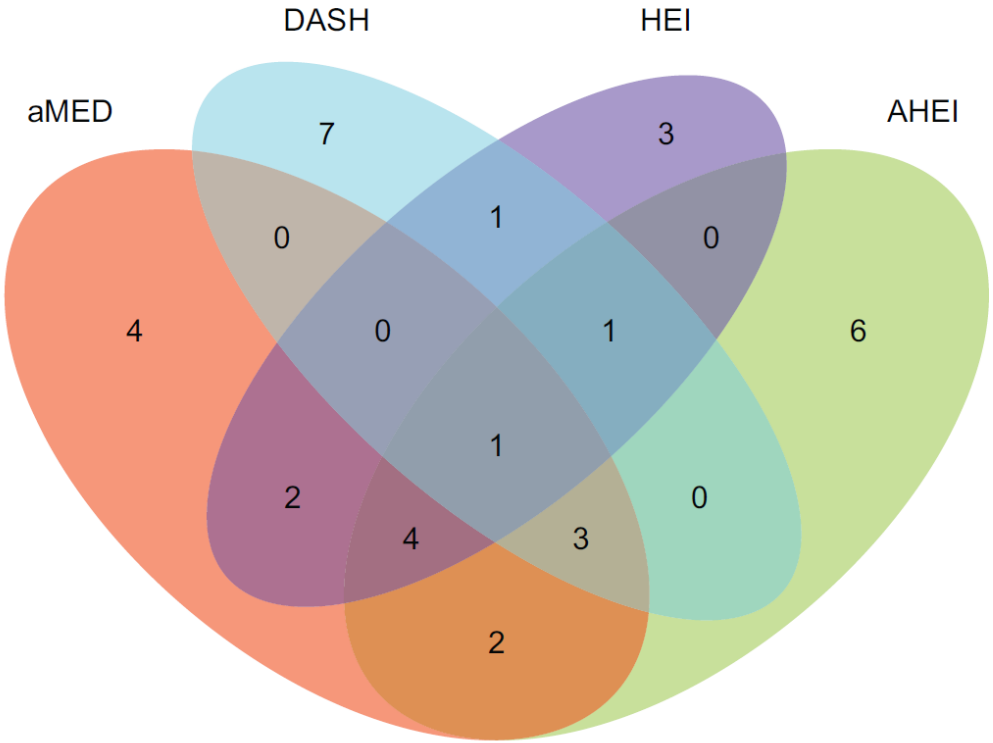

**Evaluation of association between diet and biomarkers**

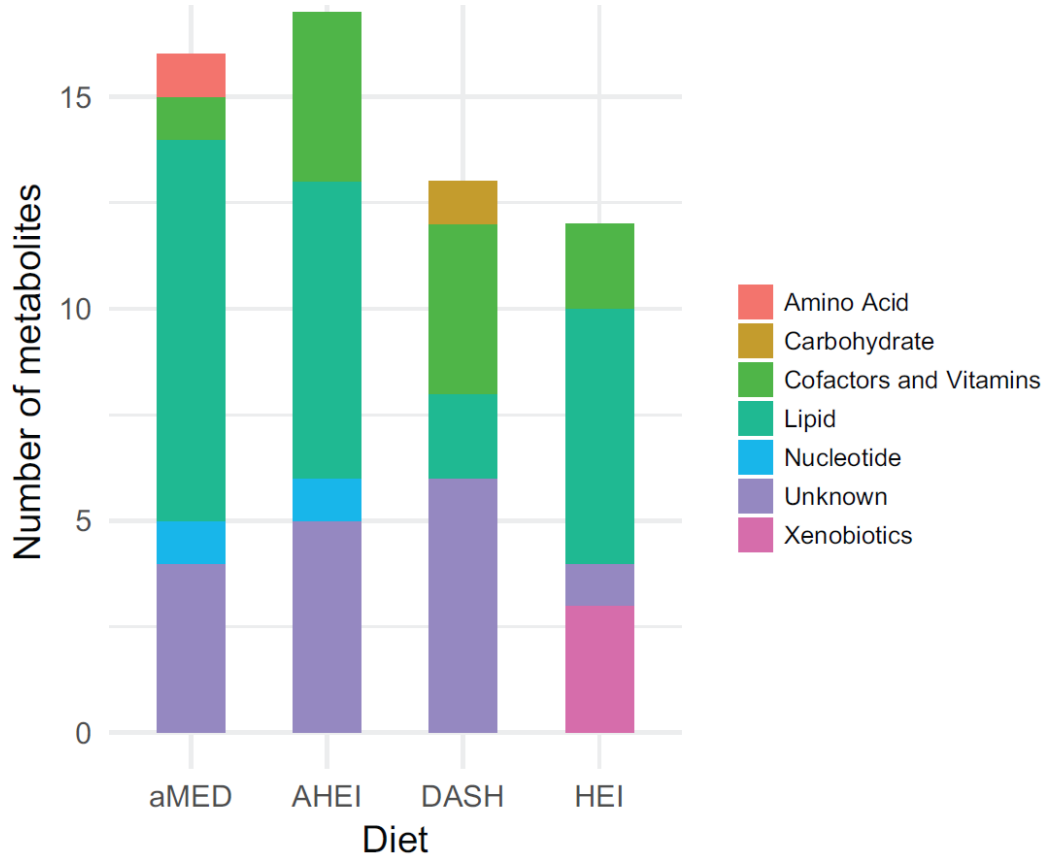
# Characterization of Diet Quality Using Dietary Indexes

| | HEI-2010 | AHEI-2010 | aMED | DASH |
|---|---|---|---|---|
| **Components / Scores** | **100** | **110** | **9** | **8-40** |
| Vegetables | + | + | + | + |
| Fruit | + | + | + | + |
| Nuts | | + | + | + |
| Legumes | | | + | |
| Fish | + | | + | |
| Whole grains | + | + | + | + |
| Total protein foods | + | | | |
| Dairy | + | | | + |
| Oils/fats | + | + | + | |
| Alcohol | | + | + | |
| Red & processed meat | | (-) | (-) | (-) |
| Refined grains | (-) | | | |
| Empty calories | (-) | | | |
| SSB & fruit juice | | (-) | | (-) |
| Sodium | (-) | (-) | | (-) |

Slide courtesy of Marian Neuhouser

# Serum metabolomic biomarkers identified healthy dietary patterns in postmenopausal women in ACS CPS-II cohort

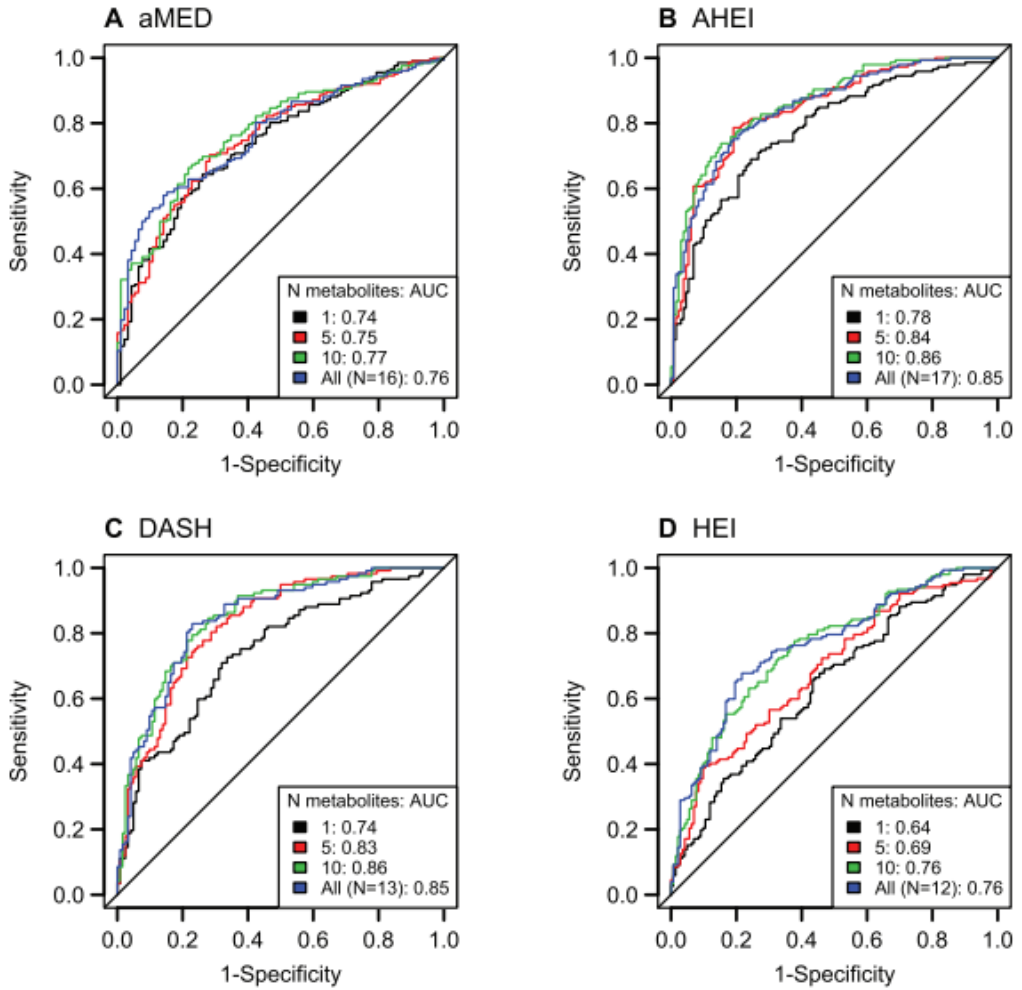


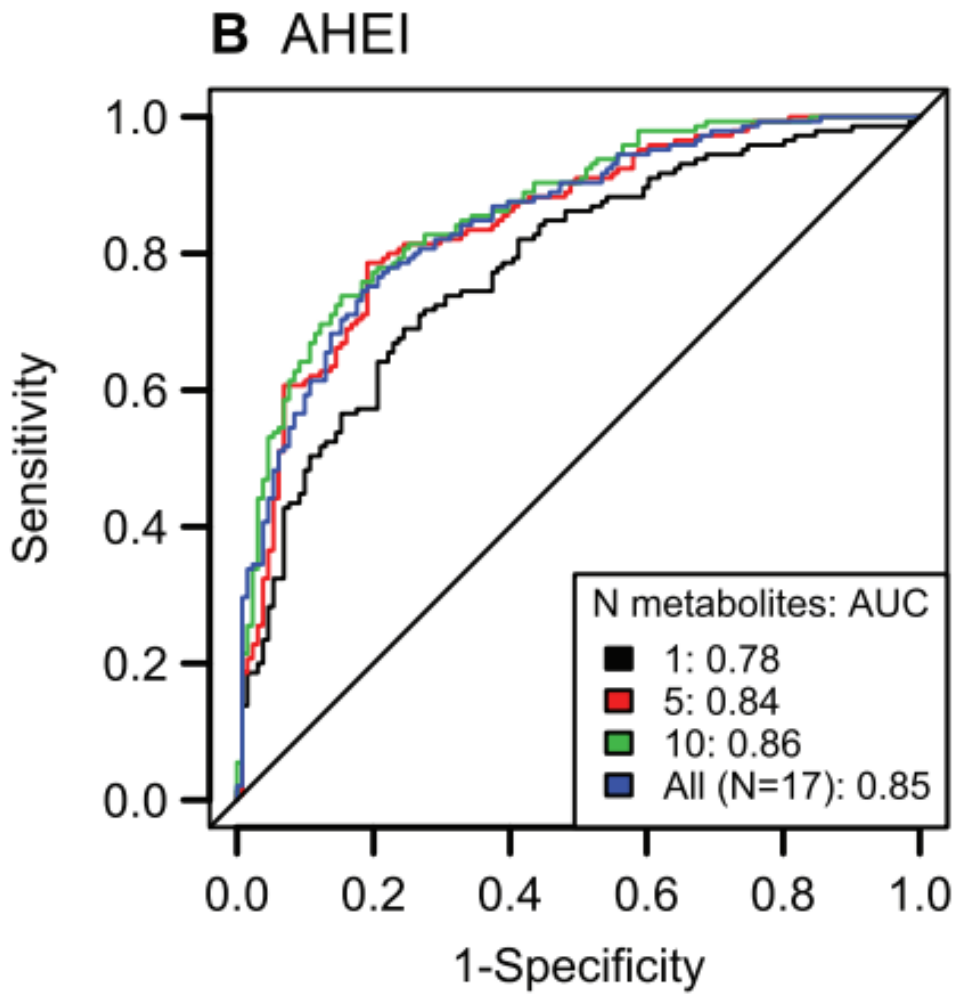




34/1186 untargeted metabolites were discriminatory
Shared metabolites across HEI and aMED reflected fish intake.

McCullough et al, *Am J Clin Nutr,* 109:1439, 2019

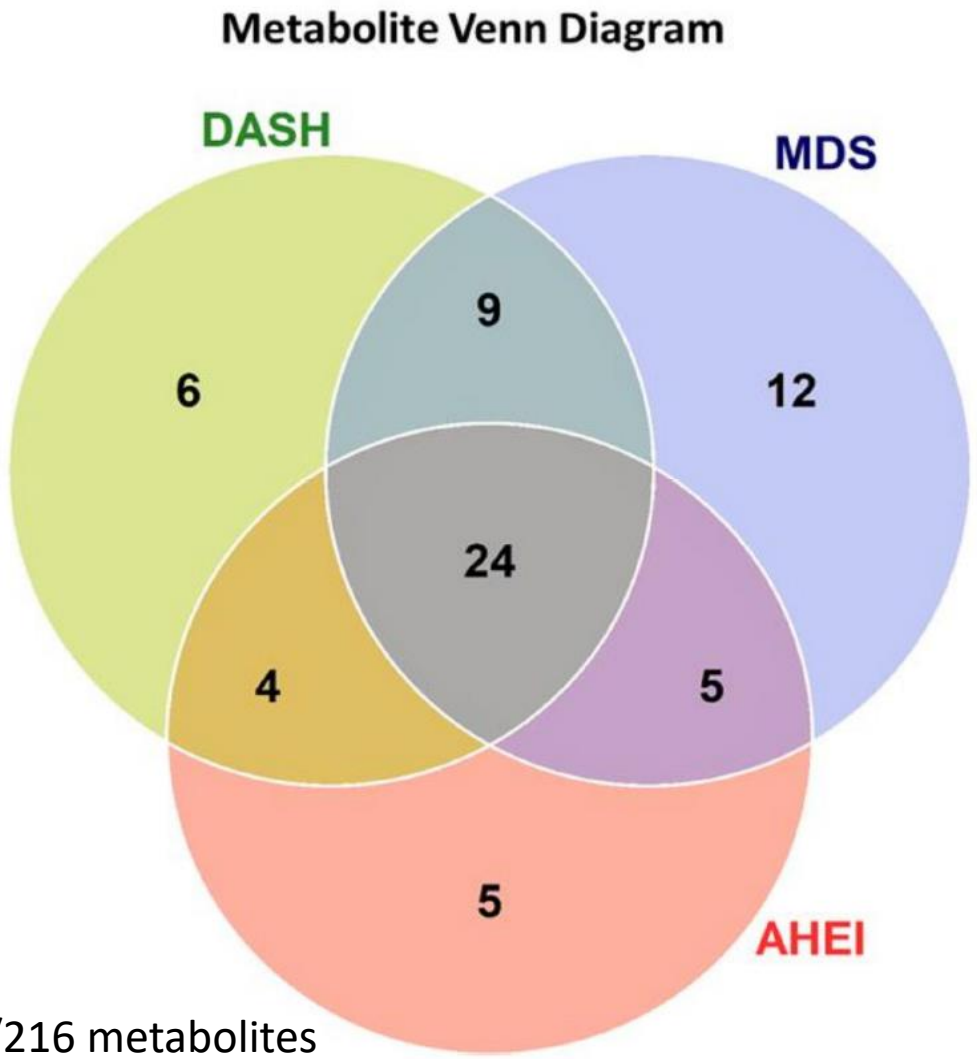
# Testing of predictive metabolites for healthy diet pattern scores in postmenopausal women in ACS CPS-II cohort



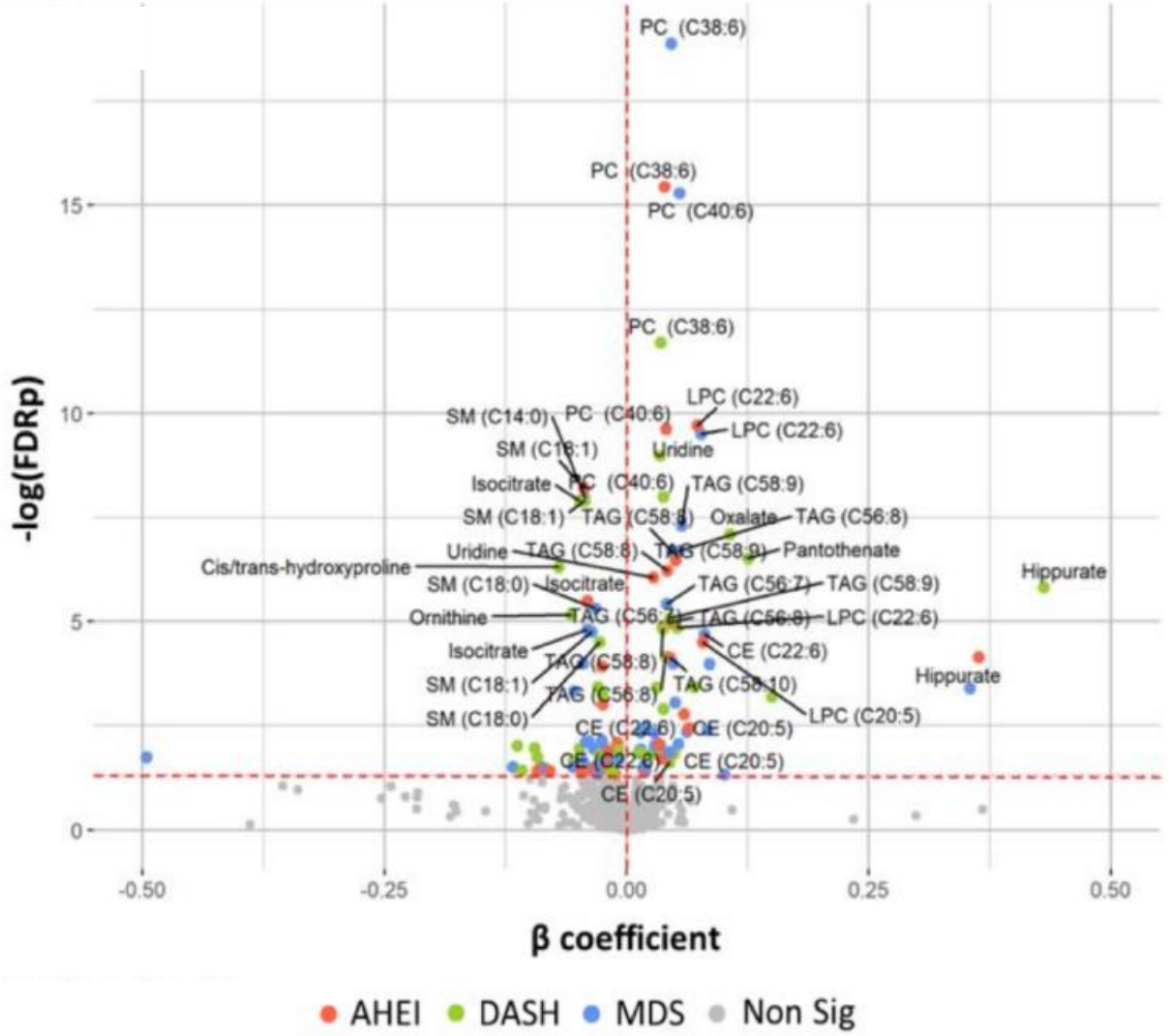




McCullough et al, *Am J Clin Nutr,* 109:1439, 2019

# Serum metabolites associated with dietary patterns in the Framingham Offspring Study (n=2284)

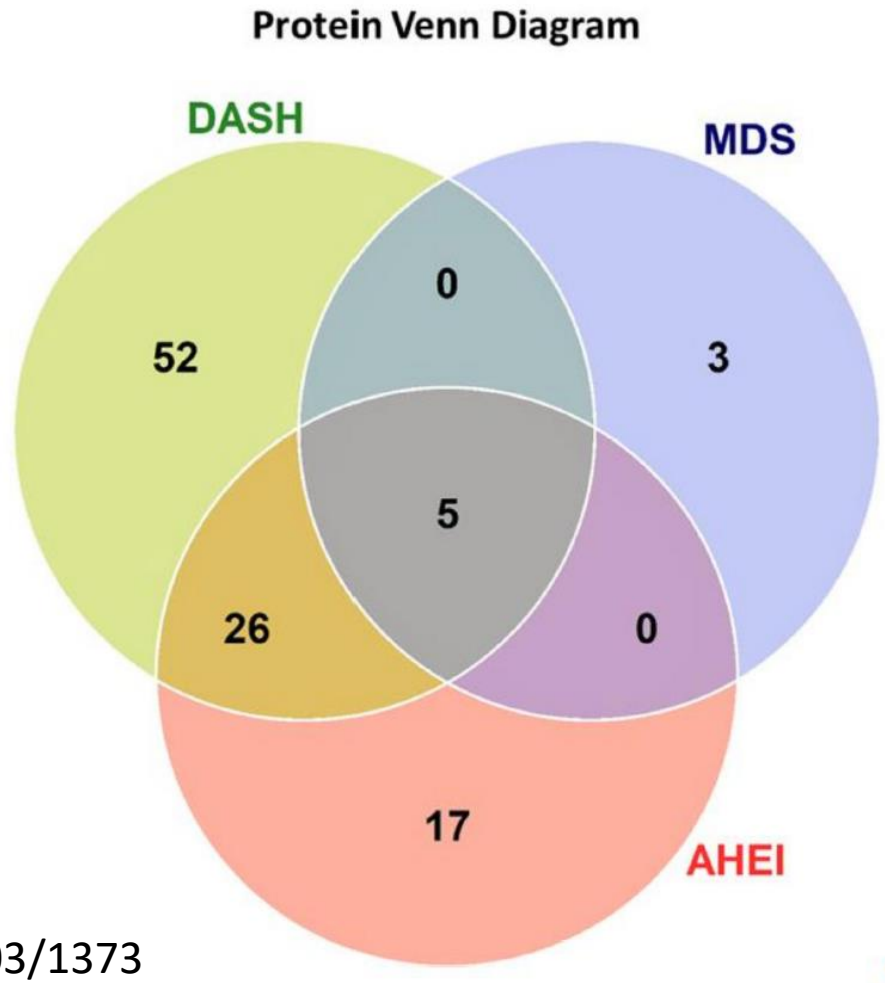



65/216 metabolites

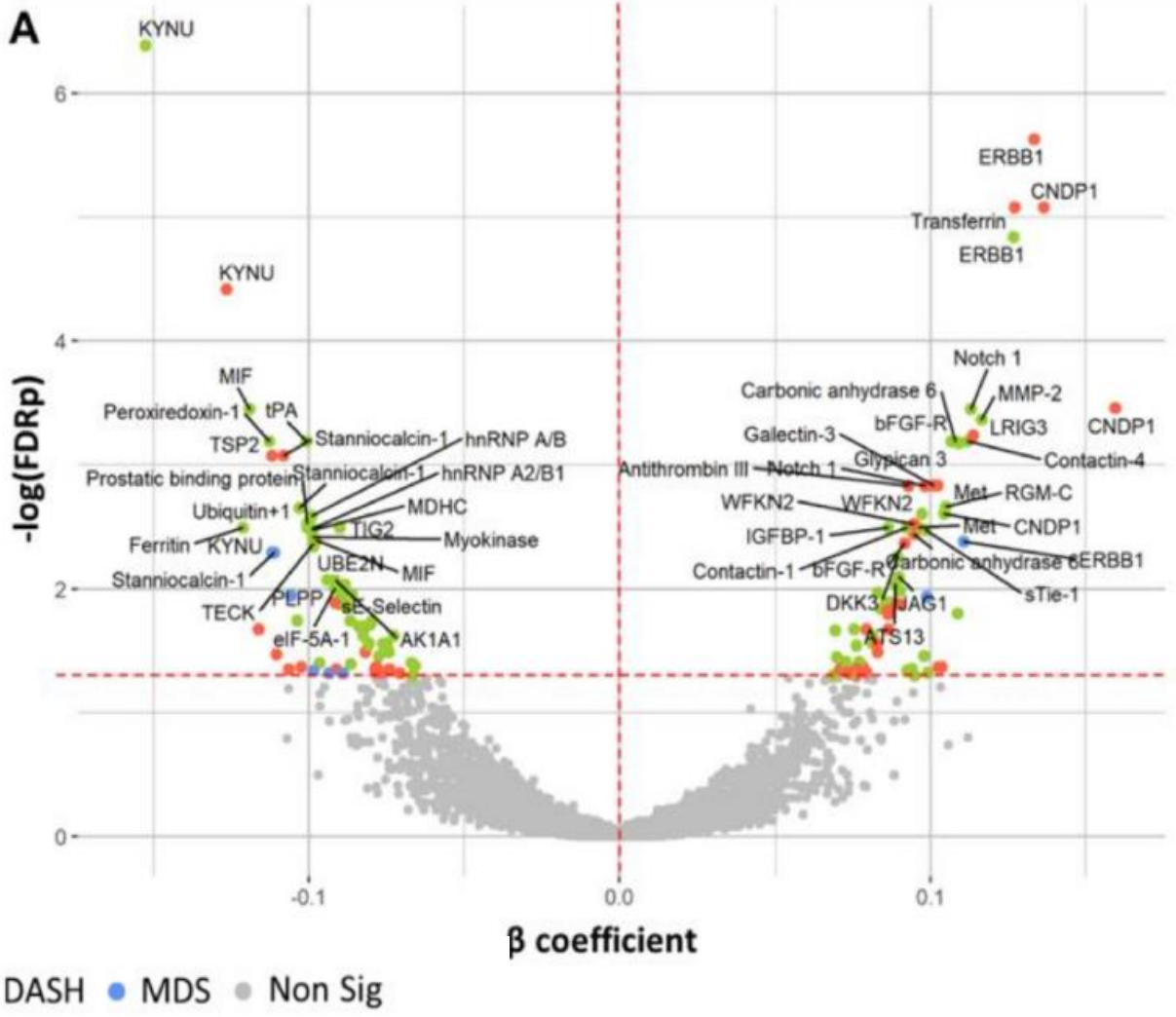



Walker et al, *Nutrients,* 12:1476, 2020

# Serum proteins associated with dietary patterns in the Framingham Offspring Study (n=1713)



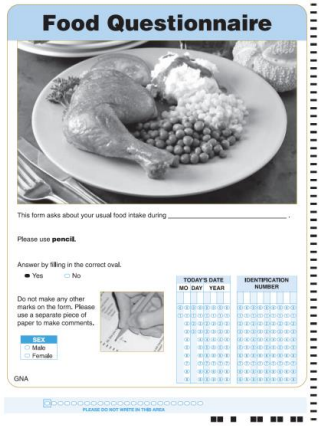

103/1373




Walker et al, *Nutrients*, 12:1476, 2020

# Gut Microbiome Measures and Diet Quality

- Diet quality has been associated with gut microbial community structure and function.
- Differential availability of substrates and other compounds to the gut microbiome as part of low- or high-quality diets is a driver of the association.




**Calculation of diet quality scores from self-reported diet**

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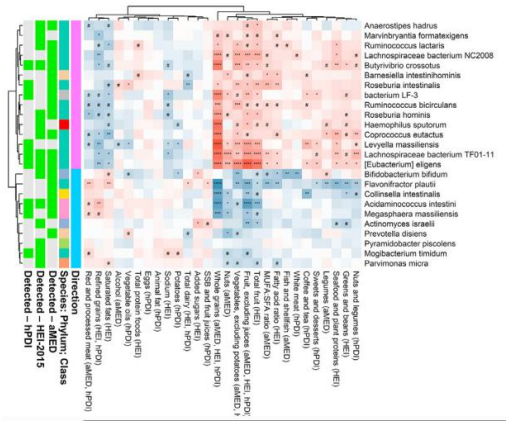
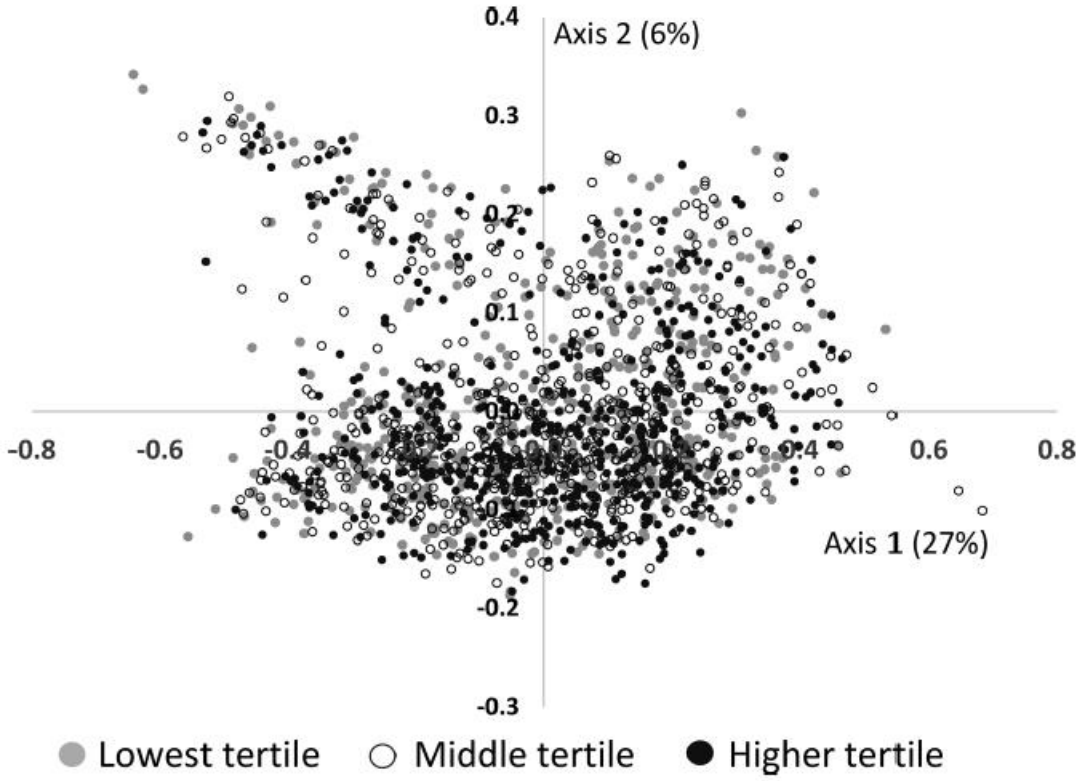
**Analysis of stool for bacterial DNA**




**Evaluation of association between diet and microbiome**

# Fecal Microbial Structure Associated with Diet Quality (HEI-2010)




The Multiethnic Cohort Study

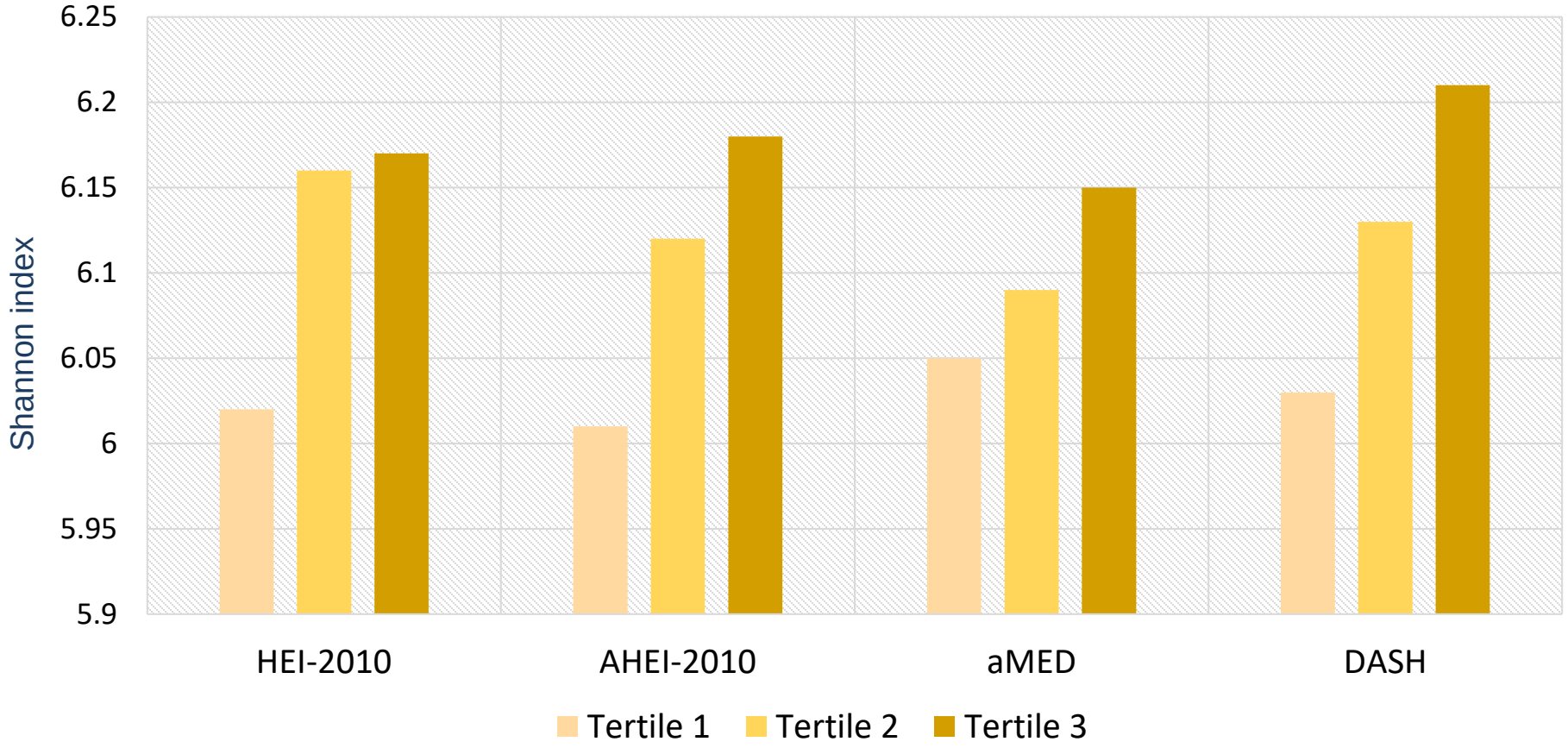
UNIVERSITY OF HAWAI'I CANCER CENTER

USC UNIVERSITY OF SOUTHERN CALIFORNIA

- 1735 participants in the Multiethnic Cohort Study
- PCA showed substantial overlap in microbial communities across diet quality, but overall significant difference between lowest and highest diet score tertiles ($P<1.0x10^{-8}$)
- 18 of 104 genera associated with HEI-2010
- Genera predominantly from *Firmicutes, Actinobacteria*, and *Proteobacteria* phyla.

Maskarinec et al, *J Nutr*, 2019

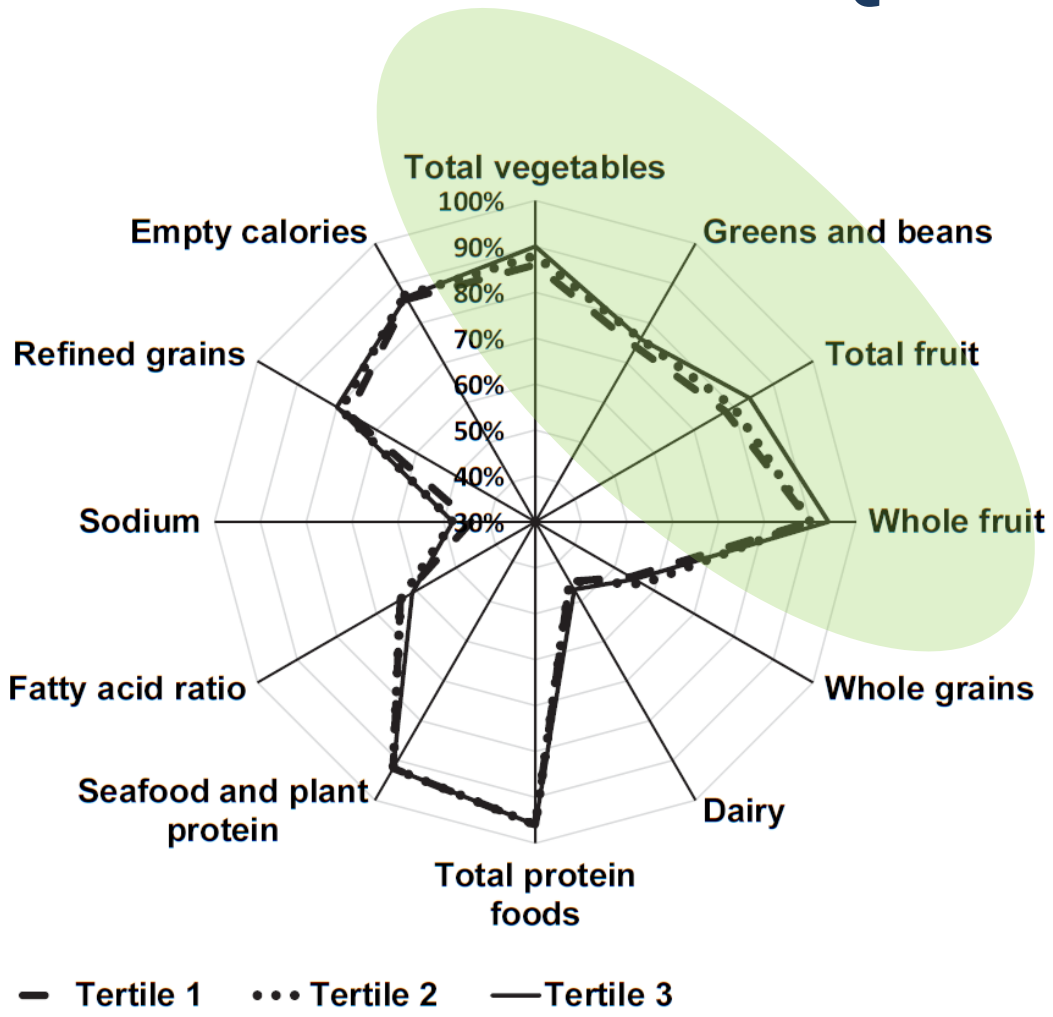
# Higher Diet Quality in Diet Patterns is Associated with Greater Fecal Microbial Diversity




Significant association with diet both at clinic visit and cohort entry 20 years earlier.

Maskarinec et al, *J Nutr*, 2019

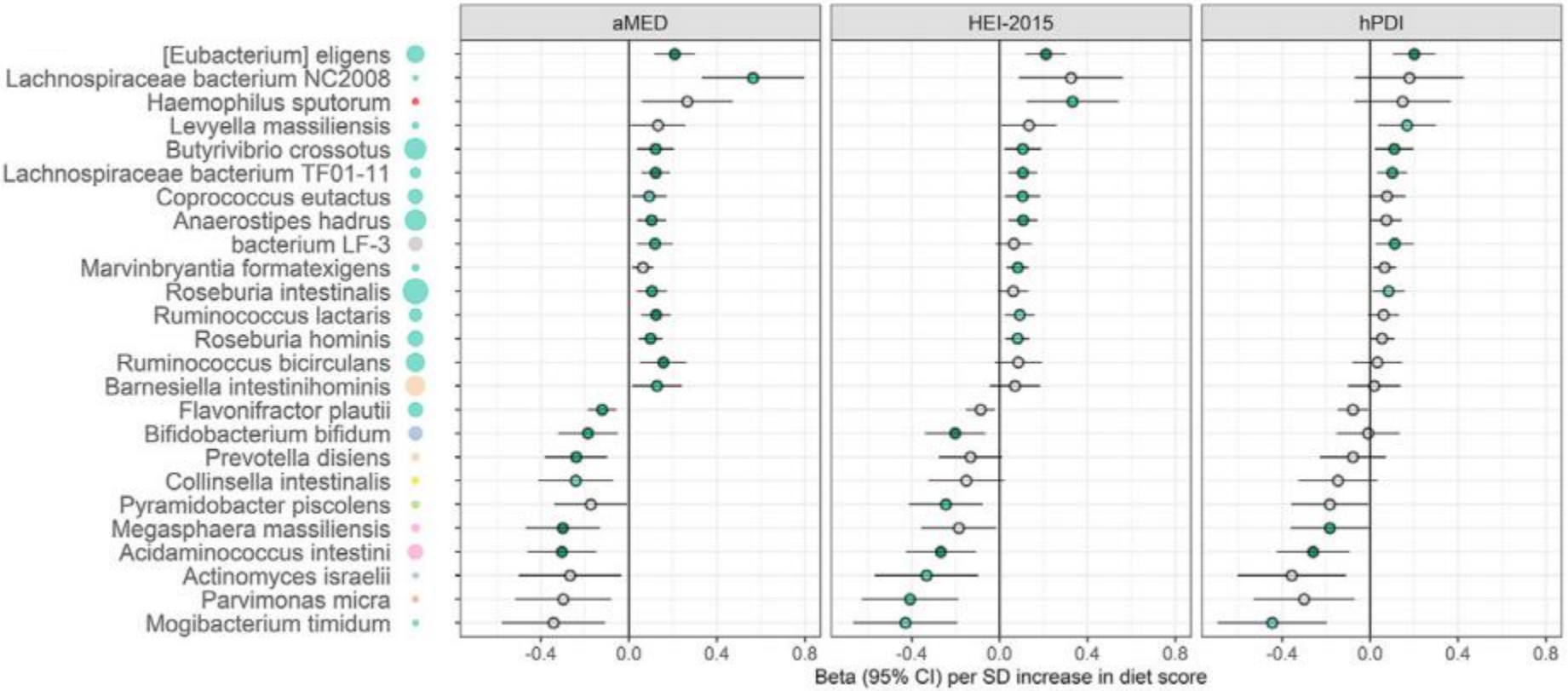
# Fecal Microbial Diversity and Structure Associated with Diet Quality




- Higher diet quality was associated with greater microbial community diversity.
- Intake of fruit and vegetables was an important contributor to the diversity.

Maskarinec et al, *J Nutr*, 2019

# Healthy Diet Patterns and Gut Microbiome in the Hispanic Community Health Study/Study of Latinos

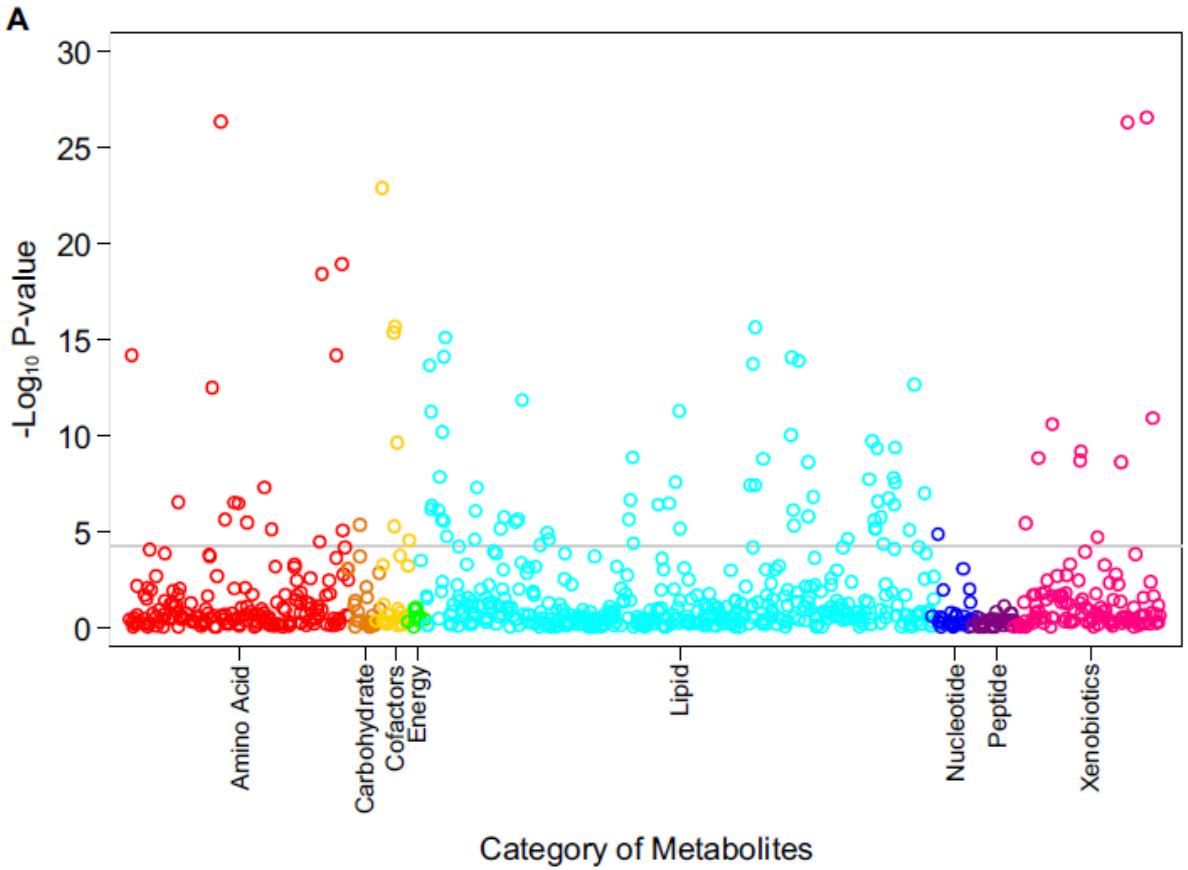


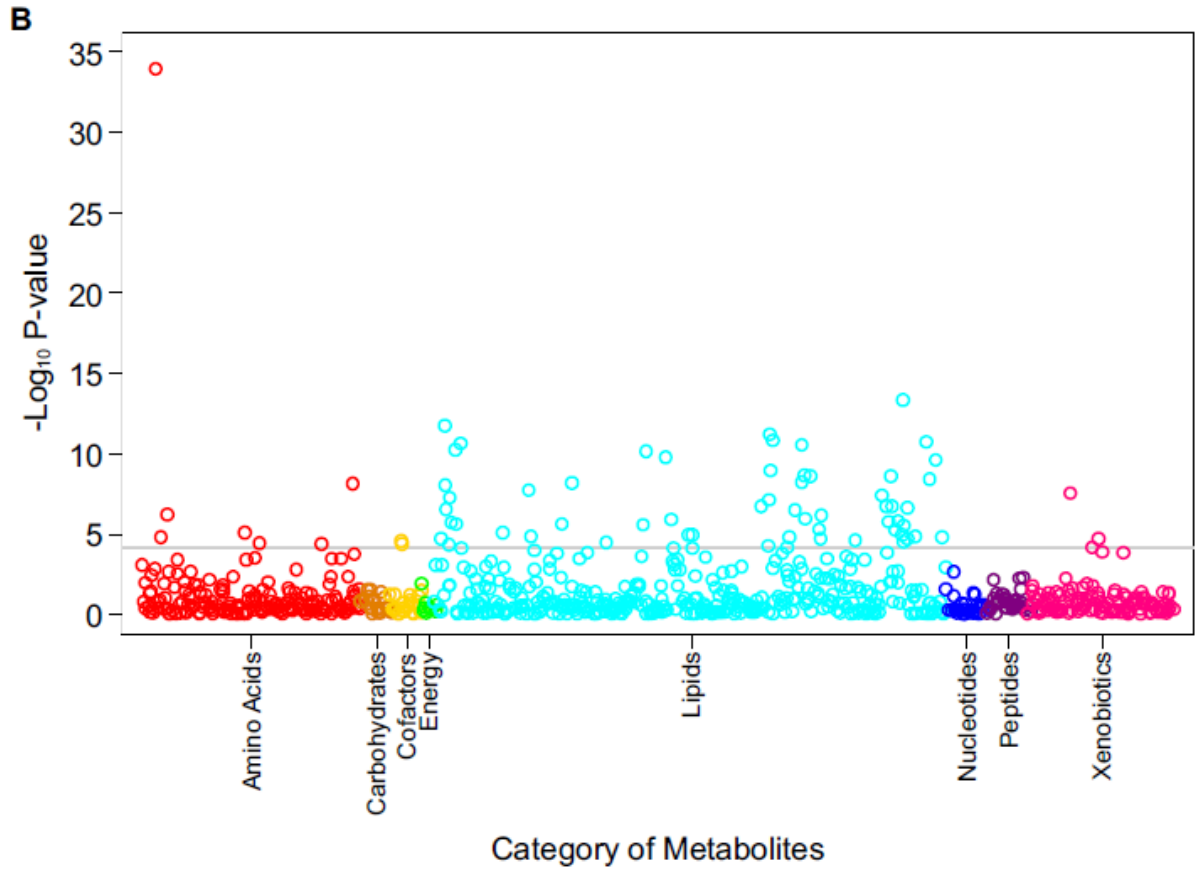

- 2444 US Hispanic/ Latino adults
- Healthy diet patterns associated with higher abundance of fiber-fermenting Clostridia species
- Whole grains, fruit and vegetables strongest drivers
- No association with alpha-diversity

Peters et al, *Am J Clin Nutr* 117:540, 2023

# Diet Quality and Biomarkers of Dietary Exposure in Intervention Studies

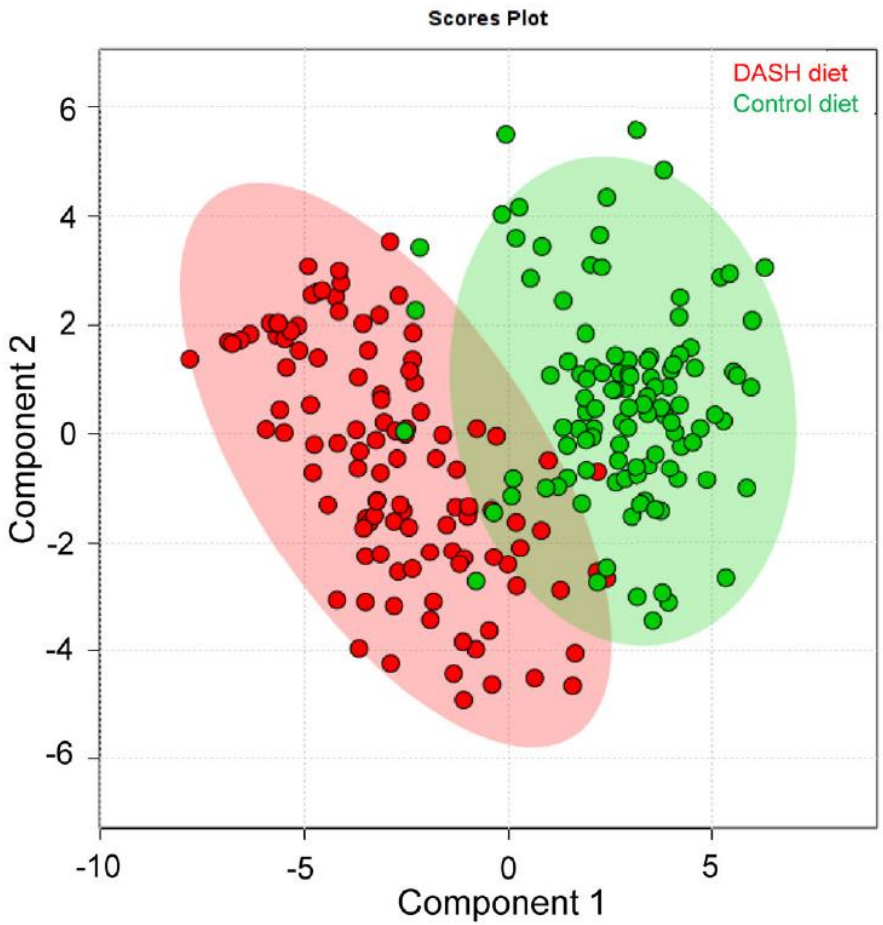
# Serum metabolites distinguished 8-week intake of DASH diet from Control (A) and Fruit & Vegetable (B) diets in controlled feeding study

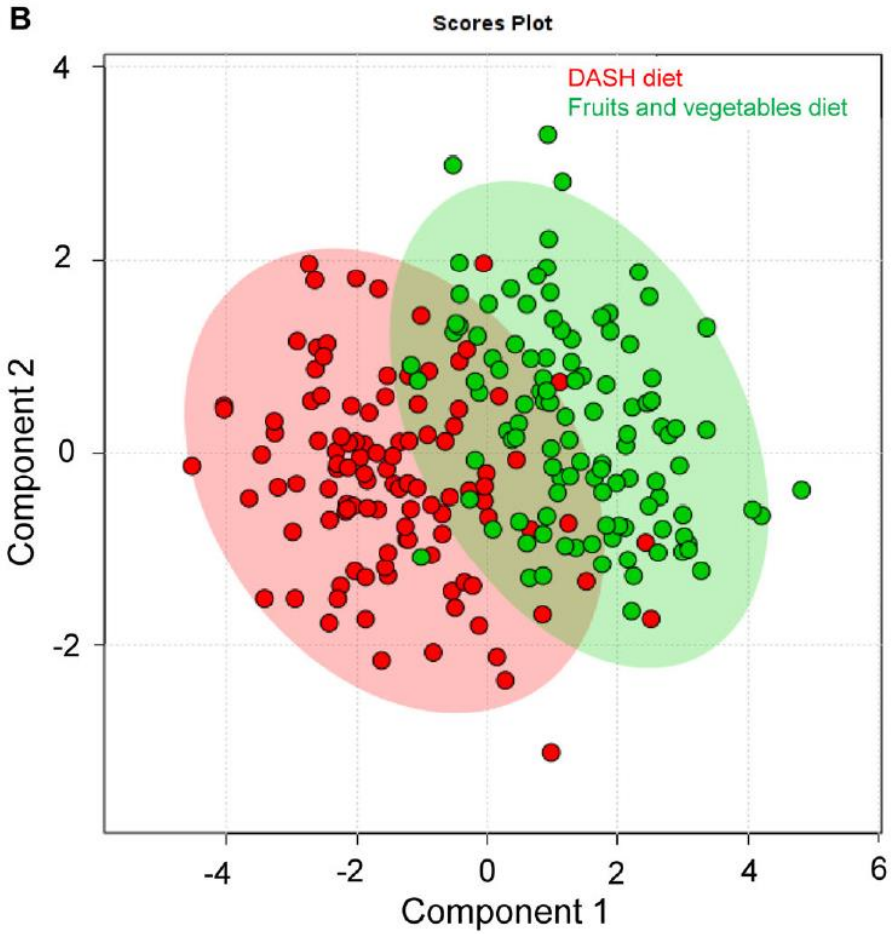



Rebholz et al, *AJCN*, 108:243, 2018

# Serum metabolites distinguished 8-week intake of DASH diet from Fruit & Vegetable and Control diets in feeding study




- Potential for developing measures of adherence for behavioral interventions.

Rebholz et al, *AJCN*, 108:243, 2018

# *Dietary Biomarker Discovery in WHI:* Nutrition and Physical Activity Assessment Study Feeding Study (NPAAS-FS)

Marian Neuhouser

Ross Prentice

THE WOMEN'S HEALTH INITIATIVE

| | | |
|---|---|---|
| **Anthropometry**<br>**Fasting blood draw**<br>**Pre-DLW spot urine**<br>**DLW dosing**<br>**Complete FFQ and other questionnaires** | **2-week controlled diet** | **24-hr urine**<br>**Weight**<br>**Fasting blood draw**<br>**2 spot urines**<br>**Indirect calorimetry** |

- 153 post-menopausal women from WHI cohort
- 2-week feeding of diet mimicking women's habitual diets
- Biomarkers:  doubly-labeled water, urinary nitrogen, serum micronutrient biomarkers, and blood and urine metabolomics

Lampe et al, *Am J Clin Nutr* 2017;105:466–75.

# Serum Measures as Biomarkers of Nutrient Intake in NPAAS-FS

| Predictive model of feeding study diet | | |
|---|---|---|
| **Nutrient intake** | **Biomarker + participant characteristics*** | **Model $R^2$** |
| Total energy | Ein | 0.53 |
| Total protein | Urinary nitrogen | 0.43 |
| Vitamin B12 | B12 + participant characteristics | 0.51 |
| Dietary folate equiv | Folate | 0.49 |
| α-carotene | α-carotene | 0.53 |
| β-carotene | β-carotene | 0.39 |
| Lutein + zeaxanthin | Lutein + zeaxanthin | 0.46 |
| α-tocopherol | α-tocopherol | 0.47 |
| *could include race/ethnicity, BMI, supplement use recreational physical activity, education | | |

Lampe et al, *Am J Clin Nutr* 2017;105:466–75.

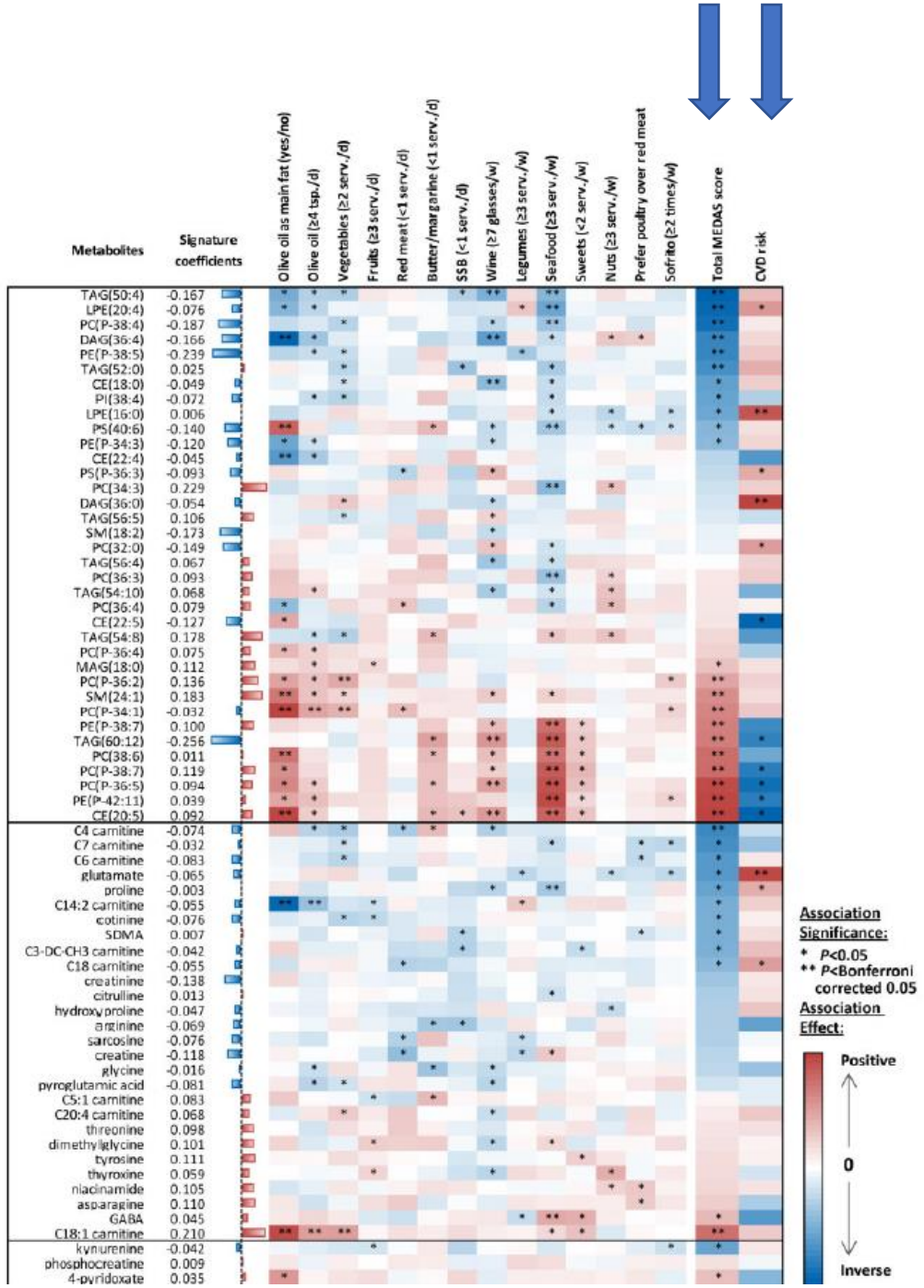
# Biomarker Characterization of Dietary Patterns in Postmenopausal Women in WHI

| Dietary Pattern | β (SE) | $R^2$ | Cross-Validated $R^2$ |
|---|---|---|---|
| HEI-2010 | | | |
| Intercept | 4.312 (0.010) | | |
| Log(β-carotene)[b] | 0.064 (0.019) | 0.10 | |
| Log(γ-tocopherol)[b] | −0.017 (0.018) | 0.04 | |
| Log(urinary sodium) | −0.073 (0.028) | 0.001 | |
| Log(urinary potassium) | 0.134 (0.037) | 0.05 | |
| Log(fatty acid 15:0) | −0.096 (0.080) | 0.03 | |
| Log(fatty acid 16:1 n-7c) | −0.068 (0.039) | 0.04 | |
| Log(fatty acid 20:1 n-9c) | 0.050 (0.056) | 0.04 | |
| Log(fatty acid 22:6 n-3) | 0.031 (0.041) | 0.03 | |
| Log(fatty acid 22:5 n-6) | −0.038 (0.030) | 0.08 | |
| Log(fatty acid 16:1 n-7t) | −0.100 (0.066) | 0.03 | |
| Body mass index[c] | −0.003 (0.003) | 0.02 | |
| Total | | 0.46 | 0.40 |

**HEI-2010 and aMED analyses met the cross-validated $R^2 \geq 36\%$ criterion in stage 1, while AHEI-2010 and DASH analyses did not.**

- Blood panel of vitamins, carotenoids, and phospholipid fatty acids; 24-h urine assayed for nitrogen, sodium, and potassium.
- HEI-2010, AHEI-2010, aMED, and DASH scores calculated from feeding study intake records.
- **Stage 1**: Scores regressed on blood and urine measures for discovery of dietary pattern biomarkers.
- **Stage 2**: Regressed stage 1 biomarkers on self-reported dietary pattern scores using a FFQ, 4-d food record, and 24-hour recall in NPAAS Observational Study; all assessment methods met criteria for HEI-2010 when biomarkers were applied.
- **Next steps:** Equations developed can be used to calibrate self-reported diet in larger WHI cohorts in analyses examining associations of calibrated dietary patterns with disease outcomes.

Neuhouser et al, *Am J Epidemiol* 2021;190:2461.




# The Mediterranean diet, plasma metabolome, and cardiovascular disease risk

- Spanish PREDIMED trial (n=1859) and validation cohorts (n=6868 from US Nurses' Health Studies I and II, and Health Professionals Follow-up Study (NHS/HPFS).
- Metabolic signature, comprised of 67 metabolites, robustly correlated with diet adherence in PREDIMED and NHS/HPFS
- Signature also showed significant inverse association with CVD incidence.

Li et al, *Eur Heart J,* 41:2645, 2020

# Summary

- A variety of omics approaches have been used to identify biomarkers of dietary patterns and diet quality.
- Blood and urine metabolomic biomarkers show strong utility as objective measures of diet quality.
- Controlled feeding studies can inform interindividual variation in biomarkers and provide an approach to develop calibration equations and biomarker profiles to apply to larger cohorts.
- Gaps remaining:

  Replication in independent and ethnically diverse populations

  Longitudinal studies of relation of biomarkers to progression of chronic disease

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