Estimating adult biological age (BA) with multiple domains through a generalized structural equation model (SEM)

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The NIA Biomarker Network ANNUAL MEETING

Background

- **There is increased research by microbiologists to build a BA clock that incorporates the Microbiome. Their motivation is as follows:** "Microbiome dysbiosis is an additional hallmark of aging" (Galkin et al 2018, Huang et al 2020)
- **The Microbiome interacts with other biological systems to influence (and be influenced) by aging**:
  - Microbial alterations (dysbiosis) are known to be related to aging and breakdown of host homeostasis
  - Microbiome is involved in multiple physiological functions including:
    - immune regulation & inflammation
    - metabolic functioning (e.g., insulin resistance)
    - DNA integrity (e.g., replication errors)
    - cognitive decline (Alzheimer)
    - methylation and histone modification

Background

- **The Microbiome goes through at least four life course stages:**

(i) **Birth**: population of facultative aerobic bacteria.

(ii) **Infancy**: colonization by obligatory anaerobic bacteria during breastfeeding.

(iii) **Adulthood**: change as a result of various factors such as region of residence, behaviors, diet, physical activity, exposure to disease, medications.

(iv) **Older adulthood**: there is evidence suggesting radical alterations. In particular, decreased diversity.

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Goal

Novelty of our approach is threefold

1. **Add microbiome measures including microbial richness, diversity, and number & abundance of species as an additional set of indicators**

2. **Propose a unified methodology to include multiple domains**

3. **Train our estimate of BA on outcomes other than mortality (in progress)**

Data: Study of Health of Wisconsin, SHOW 2016-2017

- Representative sample of residents in Wisconsin in 2008
- We use sample of adults aged 18+
- Final analytic sample includes 711 participants with complete information on microbiome (411 women & 300 men)

Data: indicators

Microbiome:

Richness: observed counting of species

Evenness: species abundance (Shannon–Wiener)

Diversity: different species and their distribution (inverse Simpson)

Biomarkers (11 indicators from 5 physiological systems):

1. Metabolic

1.Glycated hemoglobin
2. Total cholesterol
3. HDL-cholesterol
4. Triglycerides

2. Cell blood count

5. White blood cells
6. Red blood cells
7. Hemoglobin
8. Platelet count

3. Cardiac system

9. Systolic blood press

4. Kidney function

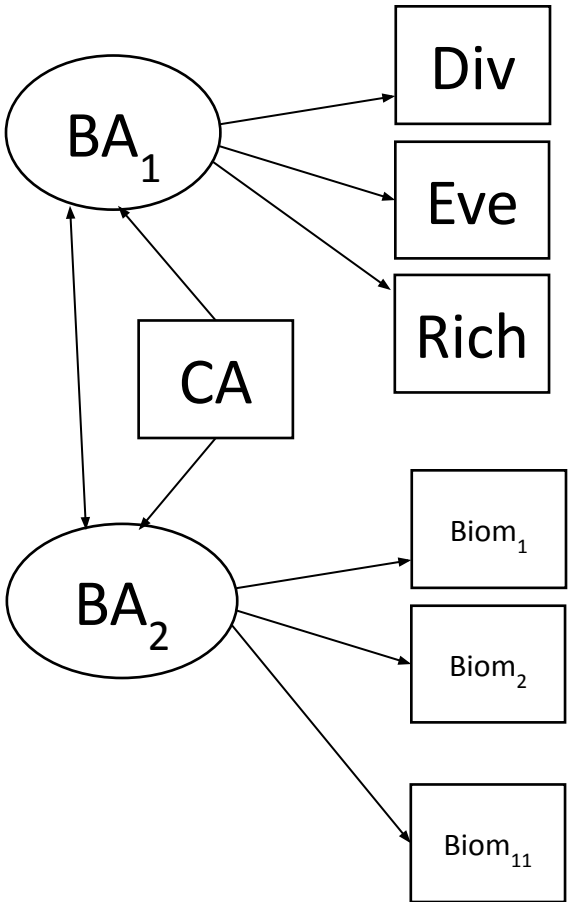
10. Creatinine

5. Lung function

11. Forced exp volume

Analytic approach

Use a structural equation model (SEM) to fully formalize the relations between two sets of latent traits, Microbiom and Biomarkers, and observables such as chronological age (CA), biomarkers and the microbiome



Div= Diversity
Eve= Evenness
Rich= Richness

$Biom_1$=Glycated hemoglobin
…
$Biom_{11}$=force exp volume

Analytic approach

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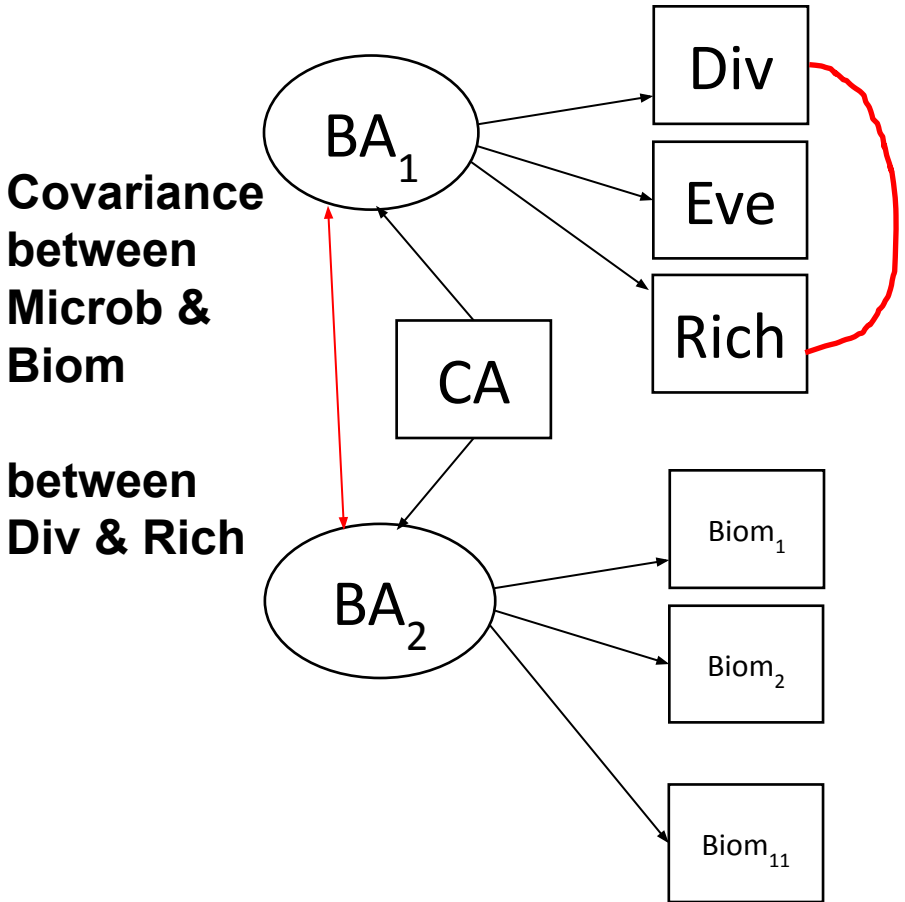
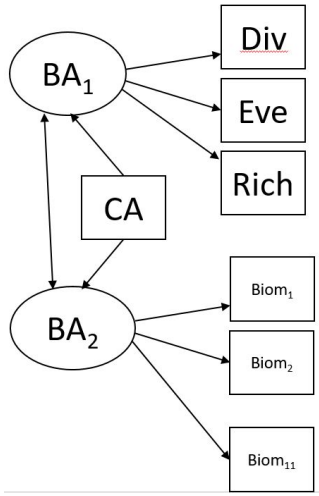


- **When we include Biom & Microb we obtain the part of Microb not related to Biom**

Analytic approach

Use a structural equation model (SEM) to fully formalize the relations between two sets of latent traits, Microbiom and Biomarkers, and observables such as chronological age (CA), biomarkers and the microbiome



Estimate two SEM models

1. Using biomarkers only
2. Using both biomarkers and microbiome

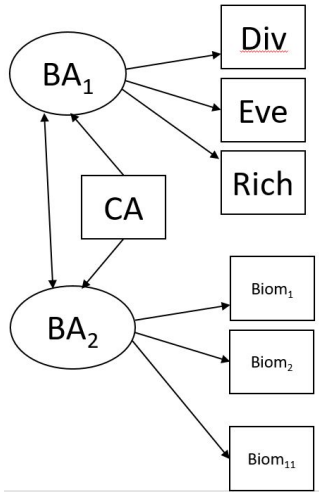
Predict factor scores (FS) from each SEM, these are unitless measures of each latent variable

The FS's can be thought of as a (conditional) mapping of the vector of unknown BA's onto a vector of real values that preserve the ranking of BA implied by CA and biomarkers/microb

Assign an "age" value by regressing the observed values of CA on FS: $CA = \alpha_0 + \beta_1 * FS + \varepsilon$
estimate BA as: $\widehat{BA} = \widehat{\alpha_0} + \widehat{\beta_1} FS$

Analytic approach

Use a structural equation model (SEM) to fully formalize the relations between two sets of latent traits, Microbiome and Biomarkers, and observables such as chronological age (CA), biomarkers and the microbiome



Four BA estimates

Estimates	Acronyms
	SEM Biom only
	FS Microb
	FS Biom
	FS Biom + FS Microb

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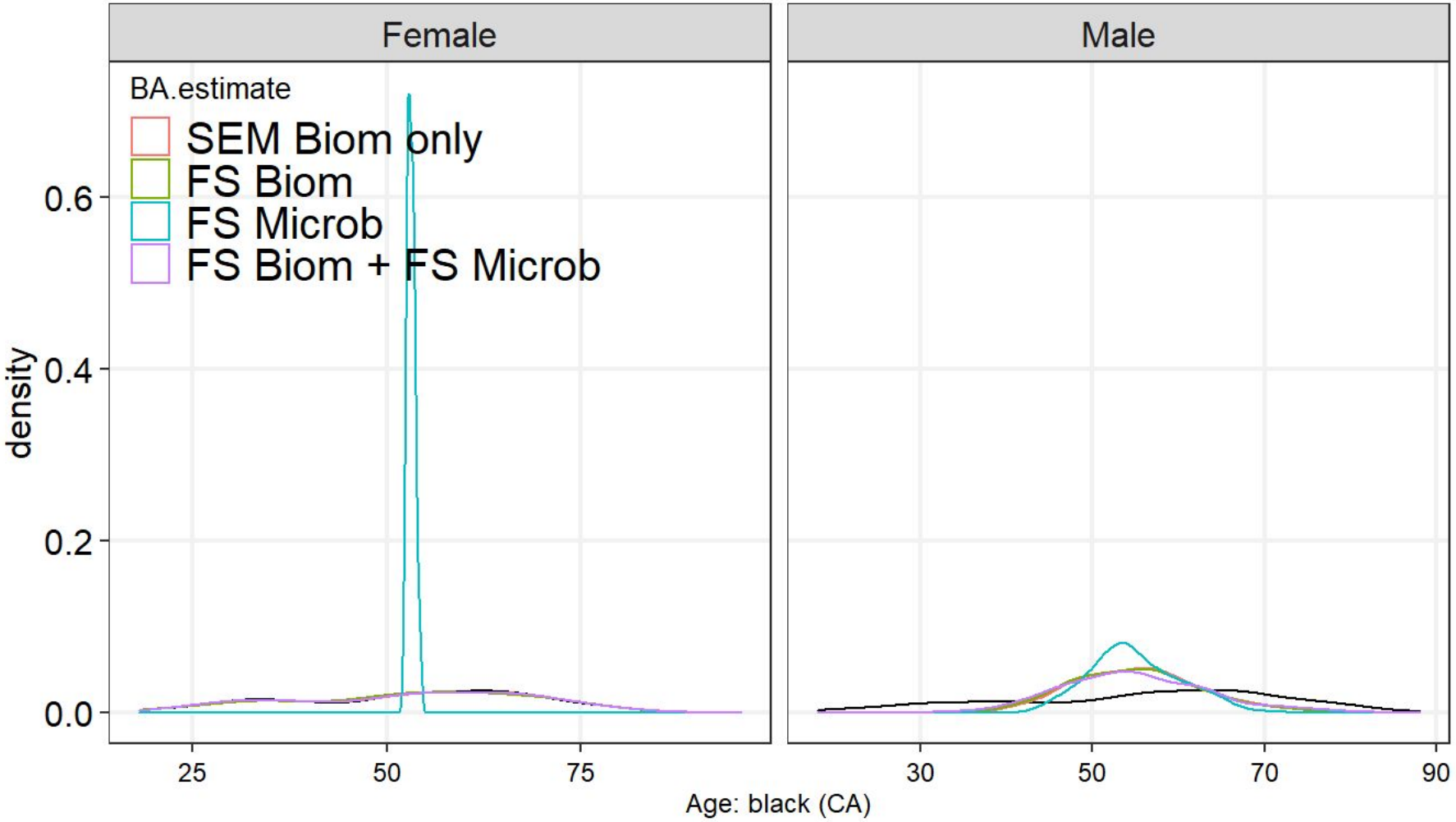
Results: Estimates of BA



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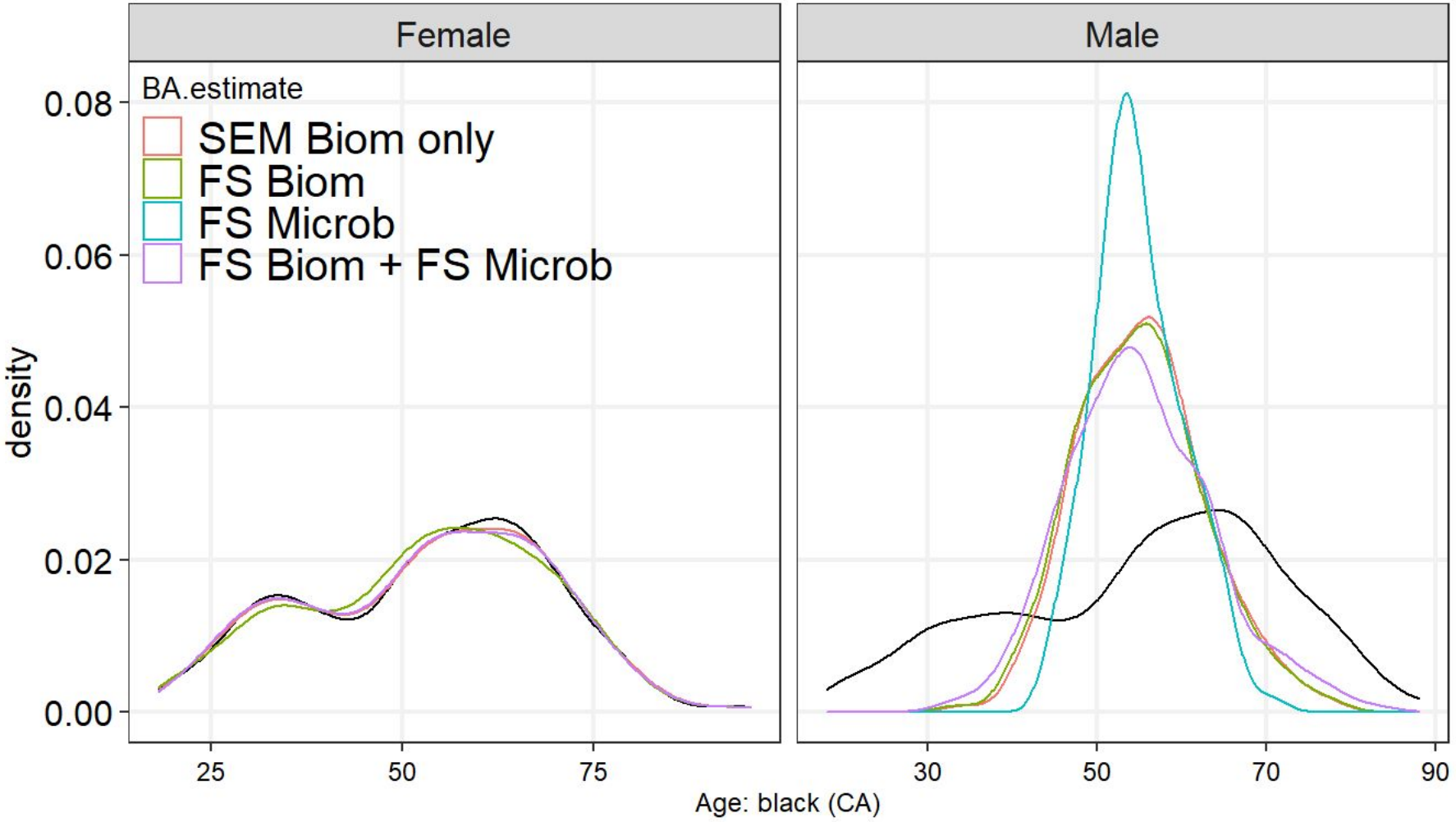
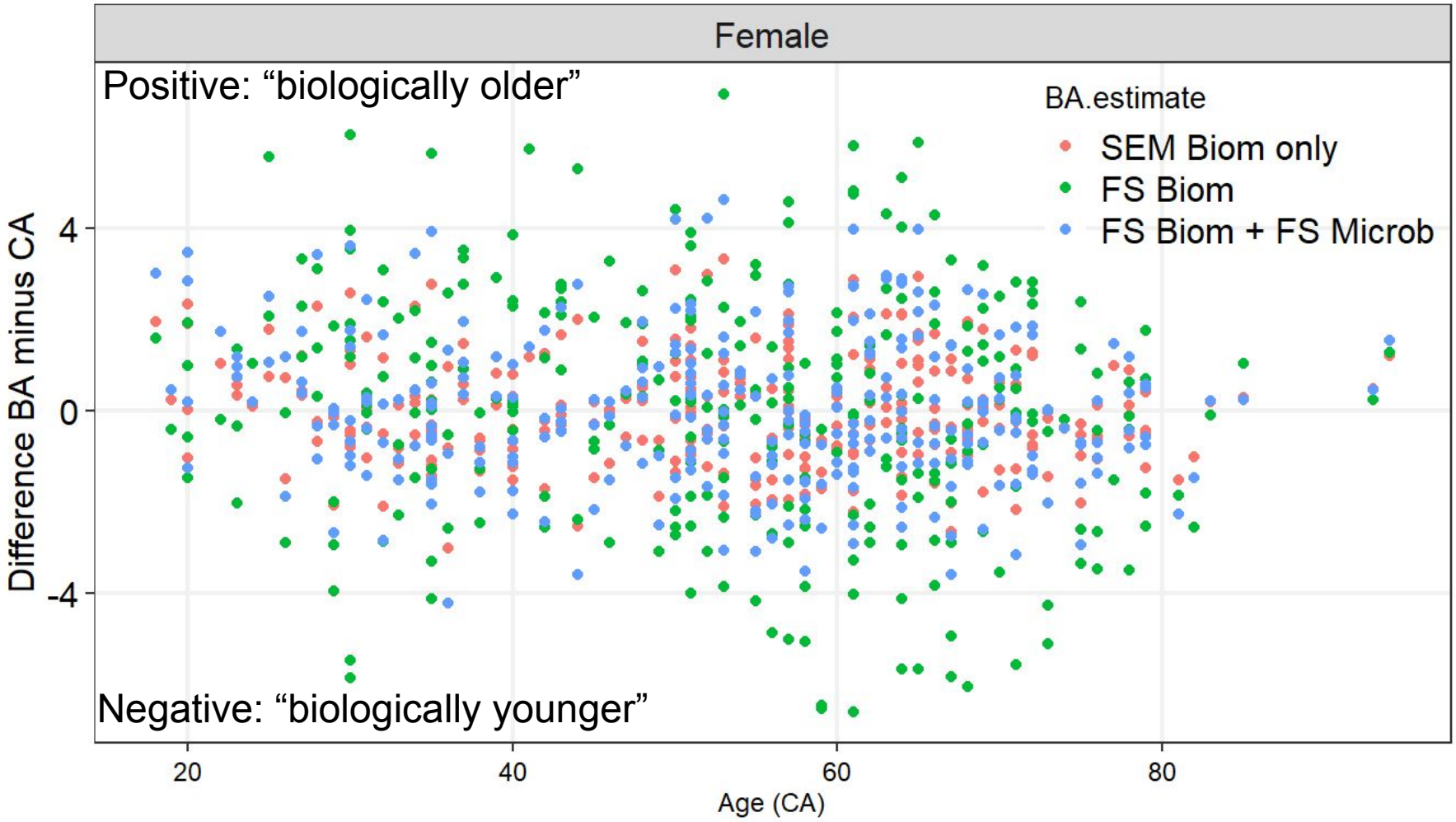
Results: Estimates of BA



Results: Difference between BA & CA
"Accelerated aging"



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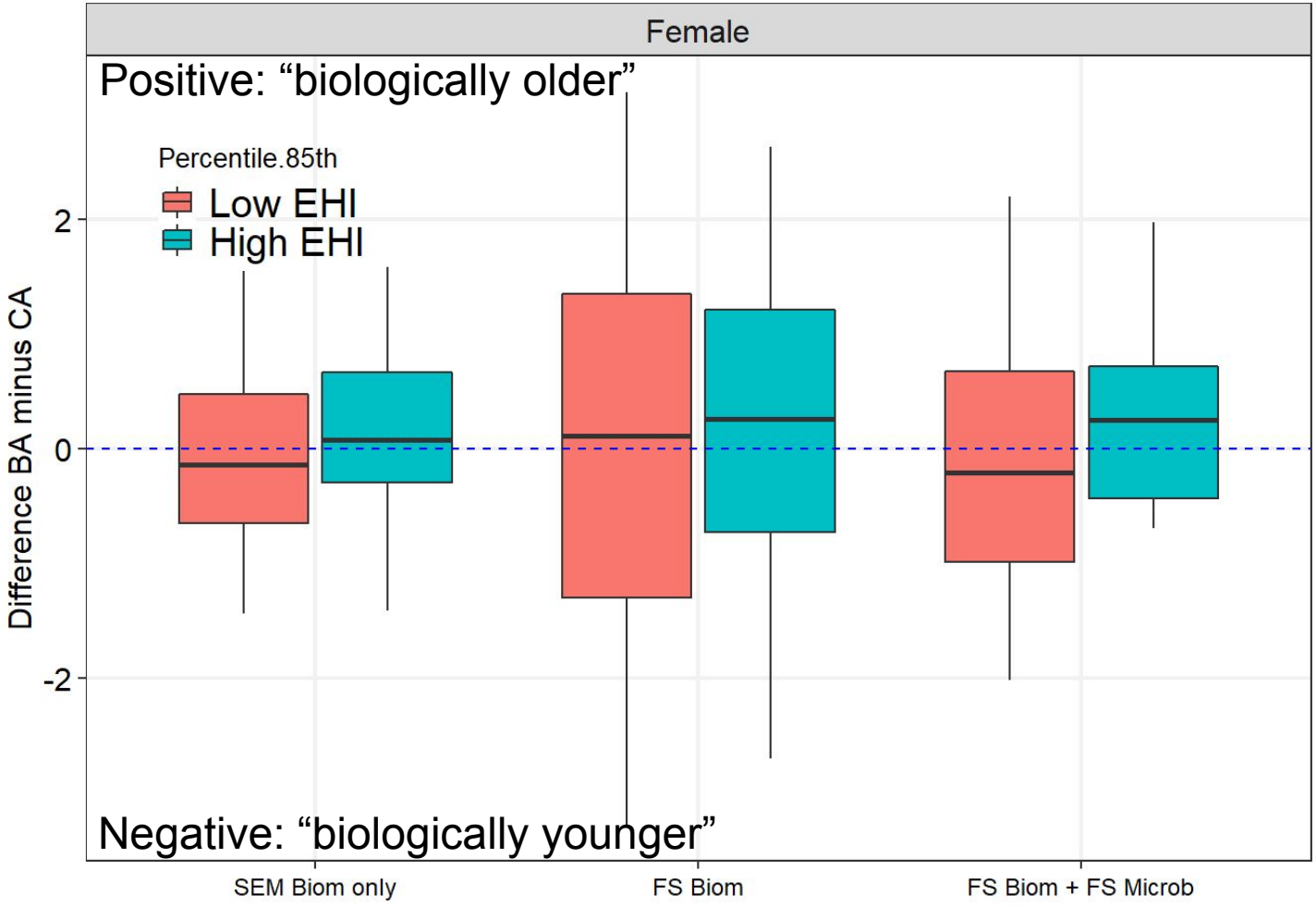
Results: Link between BA-CA and economic hardship index (EHI)



The higher the value in EHI the more economic hardship.

85th percentile
Low EHI: <85th
High EHI: >= 85th.

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Conclusions:

- This is an initial and very limited attempt to investigate the possible relation between CA and microbiome
- We are using crude measures of microbiome
- A better model has to include indicators of abundance of multiple taxa of bacteria (work in progress), classified according to the physiological system with which they are thought to be related

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Conclusions:

- **Including both biomarkers & microbiome we obtain effects of the microb of physiological states that are not related to conditions reflected in biomarkers**

- **We estimate effects while controlling for other biomarkers some of which may be reflecting states induced by the microbiome itself in the recent past: this attenuates the effect of any indicator of microbiome structure**

- **Don’t yet control for use of medications (work in progress)**

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Thank you

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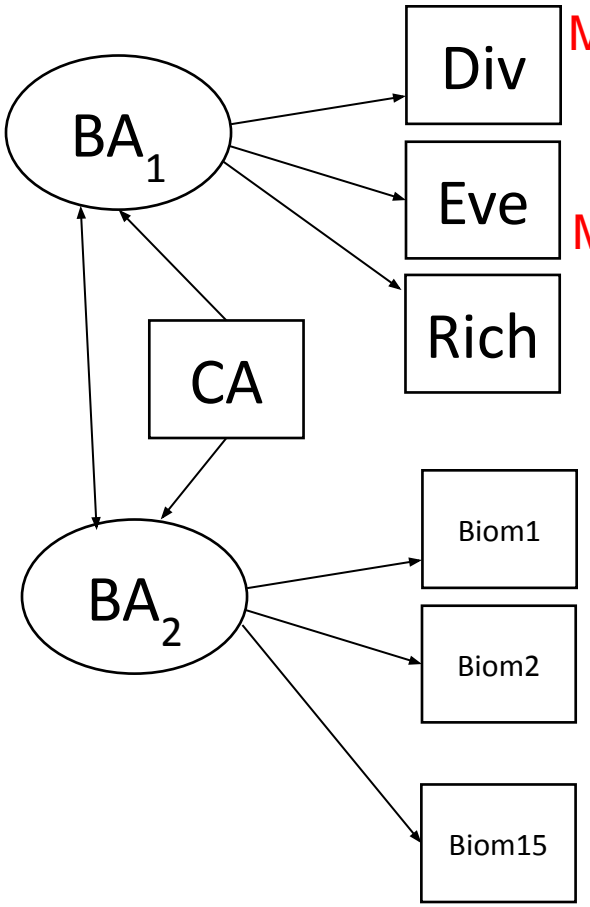
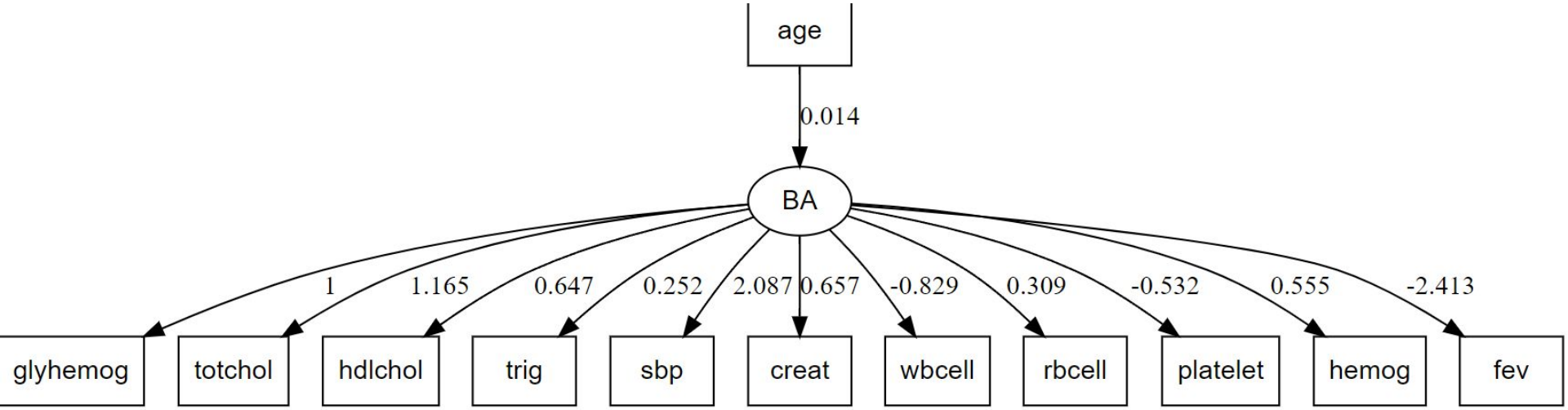
Div= Diversity
Rich = Richness
Eve= residuals from the regression
Evenness = a + b*Diversity



Mod1: Biomarkers

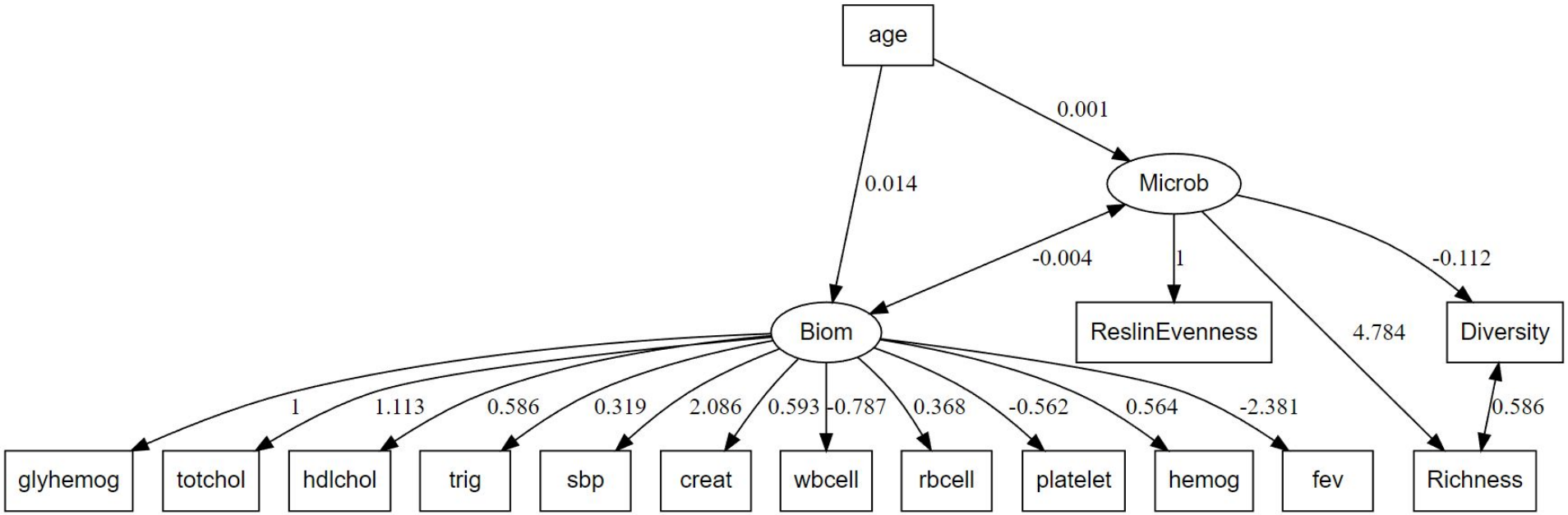
Mod2: cov(Biom,Microb) & cov(Rich,Div)

Mod1: Biomarkers



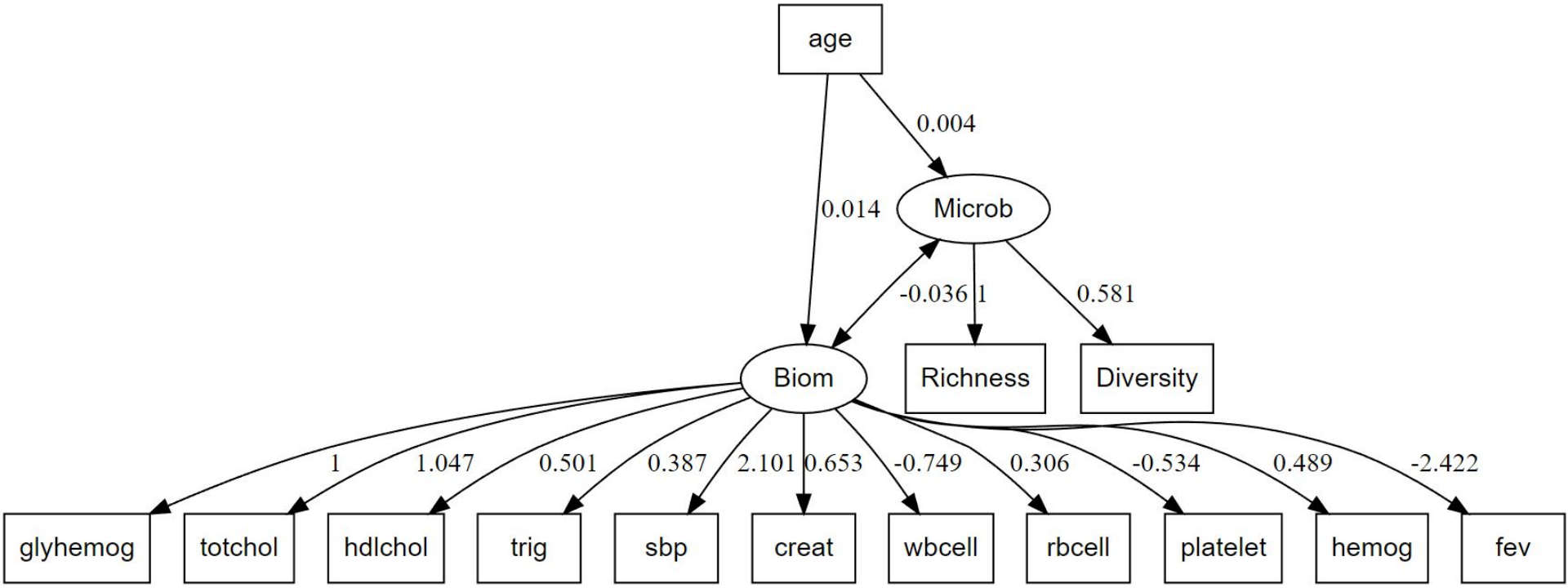
Div= Diversity
Rich = Richness
Eve= residuals from the regression
Evenness = a + b*Diversity

Mod2: cov(Biom,Microb) & cov(Rich,Div)
Males



Div= Diversity
Rich = Richness

Mod3: cov(Biom,Microb)



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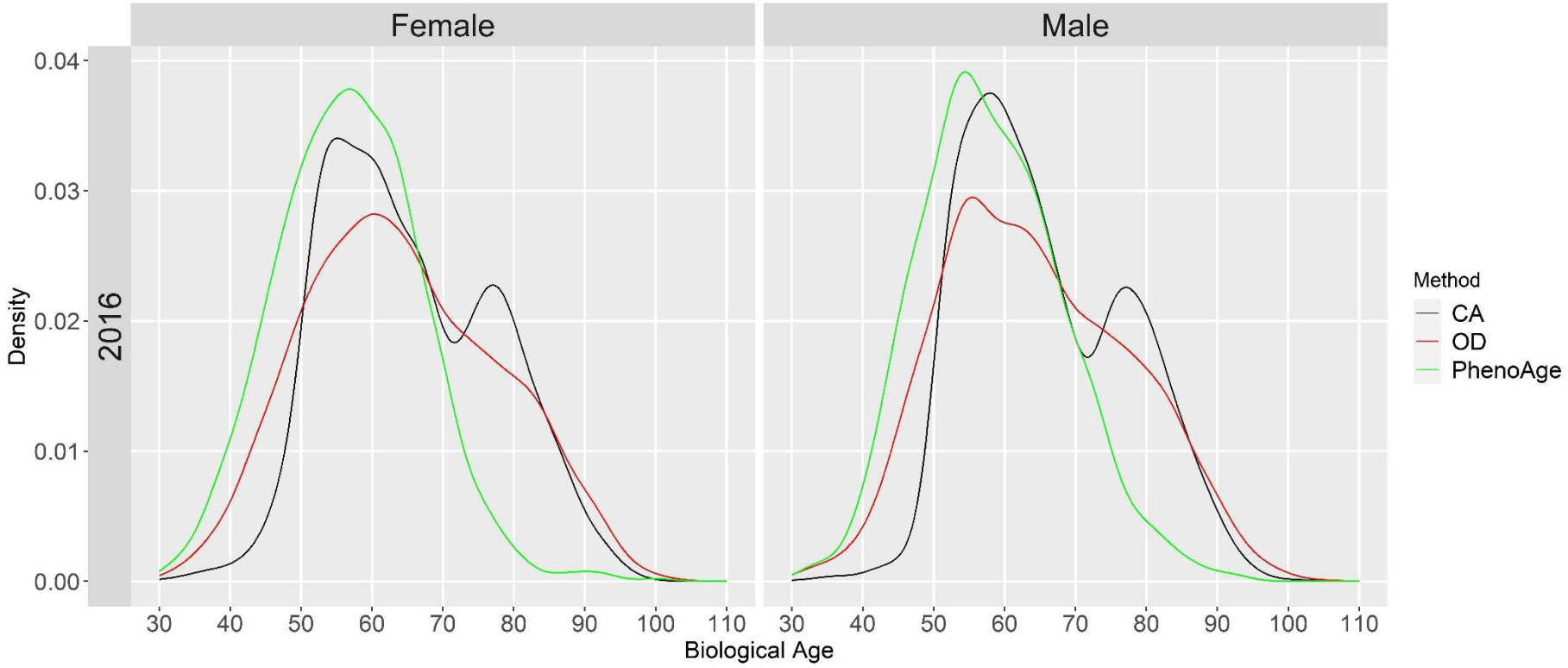
Age-pattern of predicted BA estimated from the outcome-dependent and PhenoAge for men and women in the Health and Retirement Study, 2016.