A Health Economist's Perspective on an Aging Society

Lauren L. Schmitz, PhD
Associate Professor
La Follette School of Public Affairs
University of Wisconsin-Madison
llschmitz@wisc.edu

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BIOSOCIAL EQUITY LAB

AT THE UNIVERSITY OF WISCONSIN-MADISON

Talk Overview

- Current research program
- Why is an economist interested in using DNA methylation (DNAm) data to study the social determinants of health and aging?
- Example from ongoing research with **Jennifer Smith's** lab at the University of Michigan (preliminary/in progress)



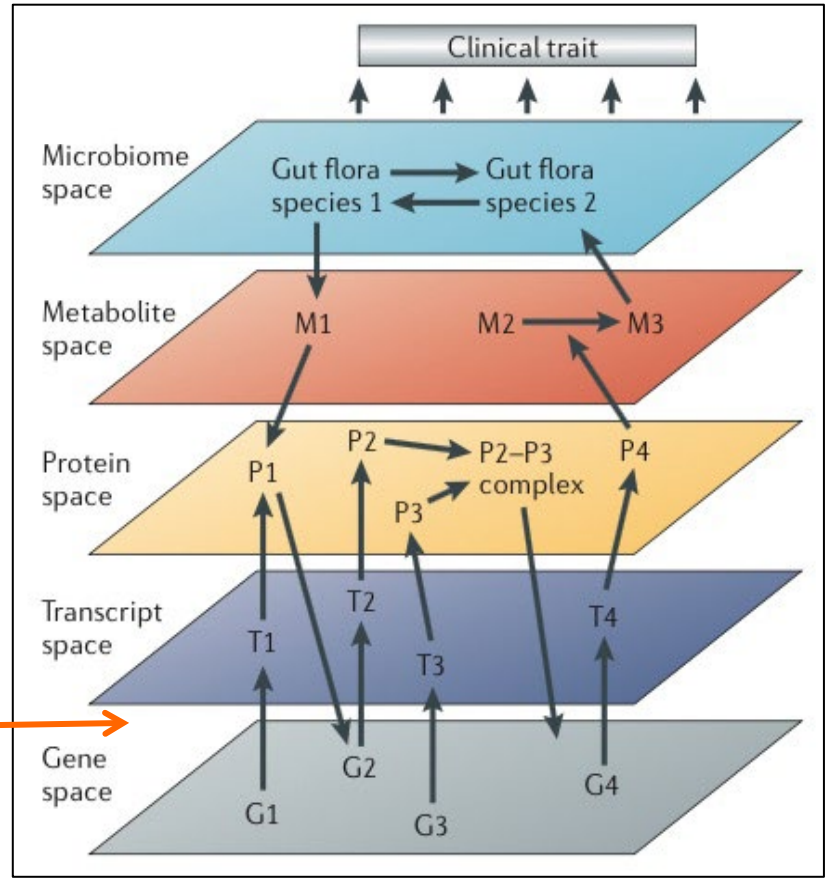
Current Research Program

How do social exposures across the life course impact health at a molecular level and speed up the aging process?

	Associational research on SES and aging	**Gene-environment interaction (G x E) research**	**Biological aging research**
Methods	• Genetic epidemiology • Epigenetic biomarkers	• Quasi-experimental methods/causal inference • Polygenic scores	• Quasi-experimental methods/causal inference • Epigenetic clocks
Examples	• Childhood/adult SES → epigenetic clocks • Epigenetic biomarkers of childhood/adult SES	• Vietnam draft • Job loss • Cigarette taxation • Lung Health Study (RCT) • Korean adoptees with random placement	• Historical shocks (Great Depression, Great Recession) • Food stamp program • Medicaid/CHIP expansions (children)

Why use DNAm to study social determinants of health?

- Mechanism for <u>stable</u> changes in gene expression that are influenced by the environment
- More proximal biologically to social exposures
  - Ability to see changes in DNAm before outcomes manifest phenotypically → earlier intervention
- DNAm effect sizes are relatively large → biomarkers can be trained in smaller samples
- Increasingly being used to construct:
  - Biomarkers of aging/health (e.g., epigenetic clocks)
  - Exposure biomarkers (e.g., prenatal smoking, lead)
  - **Proxies of clinical biomarkers (e.g., Albumin, CRP)**



Civelek, M. & Lusis, A. J. *Nat Rev Genet* 15, 34–48 (2014).

Epigenome (regulatory element) space

C. Ladd-Acosta, M. D. Fallin, The role of epigenetics in genetic and environmental epidemiology. *Epigenomics* **8**, 271–283 (2016).
Moqri et al. 2023. Biomarkers of aging for the identification and evaluation of longevity interventions. *Cell* 186: 3758-3775.

Promises of epigenetic biomarker proxies (EBPs)

"Another potential benefit of using DNAm-based biomarkers instead of plasma biomarkers is that the ***DNAm-based biomarkers are representing a longer average estimate of the biomarker concentration*** *and are not as affected by day-to-day variations that could bias results."*

GeroScience (2024) 46:1053–1069
https://doi.org/10.1007/s11357-023-00832-3

ORIGINAL ARTICLE

Higher testosterone and testosterone/estradiol ratio in men are associated with decreased Pheno-/GrimAge and DNA-methylation based PAI1

Cynthia D. J. Kusters · Kimberly C. Paul · Ake T. Lu · Luigi Ferrucci · Beate R. Ritz · Alexandra M. Binder · Steve Horvath

Core research questions

Are social gradients stronger in clinical serum markers or their corresponding epigenetic proxies?

Test associations of both **Childhood SES** and **Adult SES** (modeled separately) with:

- **Serum Biomarkers:** Directly measured clinical values
- **Epigenetic Biomarker Proxies (EBPs):** DNA methylation-based surrogates of serum biomarkers

Which markers explain more of the variation between SES exposures and later-life health?

Use the **High-Dimensional Mediation Testing (HDMT)** method to determine:

- Specific clinical biomarkers that *may* drive the SES-health relationship (not causal!)
- Use **PCA** to calculate the total proportion mediated by serum markers or EBPs

Data: Health and Retirement Study (HRS)

- Use serum biomarkers and DNAm data collected from venous blood in the 2016 wave
  - N = 3,744-3,985
- Mean age at blood collection: 69.8 (SD=9.7)
- Health outcomes are from 2020:
  - Mortality
  - Number of chronic conditions
  - Self-reported health status
  - Cardiometabolic conditions index

Epigenetic biomarker proxies (EBPs)

- Constructed 37 EBPs that overlap with serum measures in HRS
- Focused on biomarkers that clinicians commonly use for patient diagnosis, monitoring, and prognosis
- EBP algorithms are from Carreras-Gallo et al. (2024)
  - Trained in the Massachusetts General Brigham's Aging Biobank Cohort (N=4,418) and tested in the TruDiagnostic Biobank (N=15,597)

N Carreras-Gallo…JA Lasky-Su. Leveraging DNA methylation to create Epigenetic Biomarker Proxies that inform clinical care: A new framework for Precision Medicine. *medRxiv* preprint (2024).

Exposures: Child and Adult SES

Childhood SES

Average years of maternal and paternal education

Adult SES Index

Average quintile of non-missing:

- **Education years**
- **Household income**
- **Wealth**
- **Occupational prestige** (General Social Survey matched to 3-digit occupation codes)
- **Neighborhood socioeconomic disadvantage** (Summary of 6 census tract-level metrics reflecting education, occupation, income/wealth, poverty, employment, and housing)
- **Neighborhood social environment** (self-reports of aesthetic quality, safety, and social cohesion aggregated to the Census tract level)

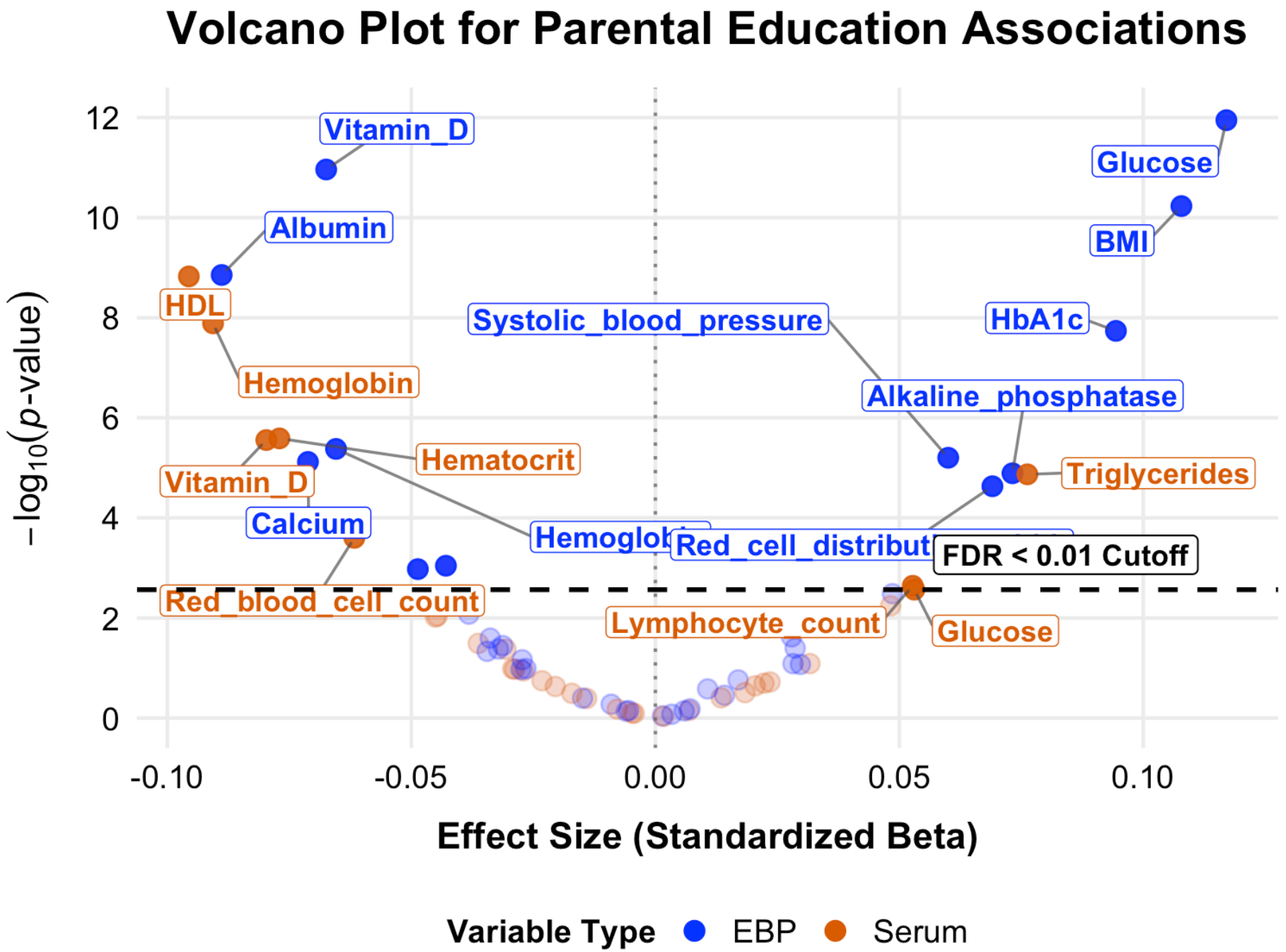
All variables except education averaged over HRS waves

Higher value = greater disadvantage

EBPs and serum correlations in the HRS

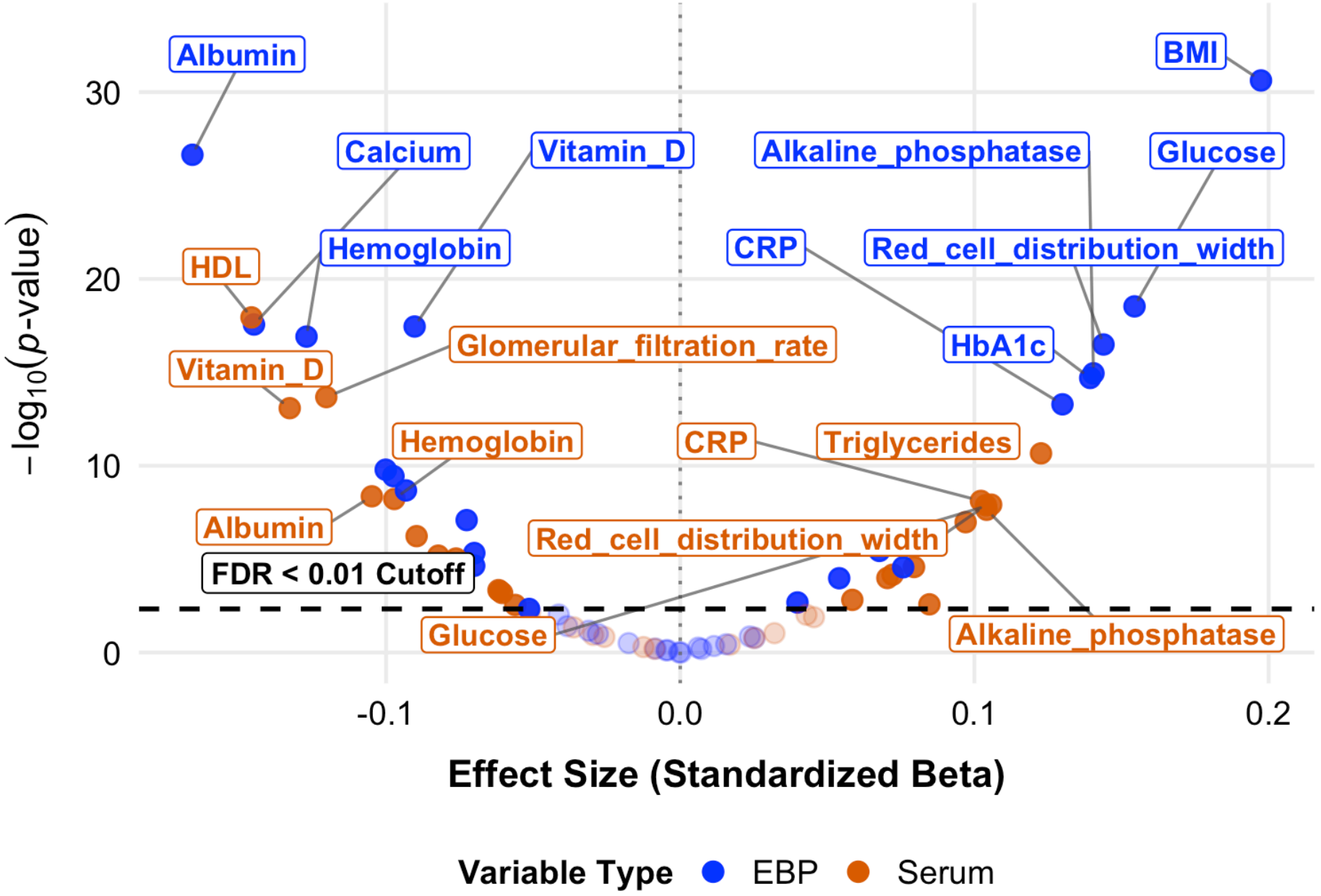
Category	Clinical biomarker	r
Anthropometric	Body Mass Index (BMI)	0.42
Blood sugar	Glucose	0.36
	HbA1c	0.33
Cardiovascular	Systolic blood pressure	0.18
Cholesterol	High-Density Lipoprotein (HDL)	0.37
	Low-Density Lipoprotein (LDL)	0.11
	Total cholesterol	0.24
	Triglycerides	0.22
Clotting	Mean platelet volume (MPV)	0.06
	Platelet count	0.28
Inflammation	C-Reactive Protein (CRP)	0.31
Kidney	Blood Urea Nitrogen (BUN)	0.42
	Creatinine	0.53
	Glomerular filtration rate (GFR)	0.44
	Albumin	0.35
	Total protein	0.15
Liver enzymes	Alanine Transaminase (ALT)	0.19
	Alkaline Phosphatase (ALP)	0.13
	Aspartate Aminotransferase (AST)	0.15
Vitamins	Vitamin D (sum of D2 and D3)	0.28

Category	Clinical biomarker	r
Liver proteins	Bilirubin	0.20
	Albumin	0.35
	Total protein	0.15
Minerals	Calcium	0.09
	Chloride	0.24
	Potassium	0.12
Red blood cells	Hematocrit	0.40
	Hemoglobin	0.48
	Mean corpuscular hemoglobin (MCH)	0.43
	Mean corpuscular hemoglobin concentration (MCHC)	0.27
	Mean corpuscular volume (MCV)	0.38
	Red blood cell count (RBC)	0.44
	Red blood cell distribution width (RDW)	0.32
White blood cells	Monocytes	0.27
	Basophils	0.20
	Eosinophils	0.69
	Lymphocytes	0.64
	Neutrophils	0.65
	White blood cell (WBC) count	0.40



- **Exposure:** Parental Education
- **Outcome:** EBP or Serum marker
- **Model covariates:** age, sex, race/ethnicity, smoking, alcohol use, BMI, and technical covariates (for EBP models only: row, column, plate)

Volcano Plot for Adult SES Index Associations

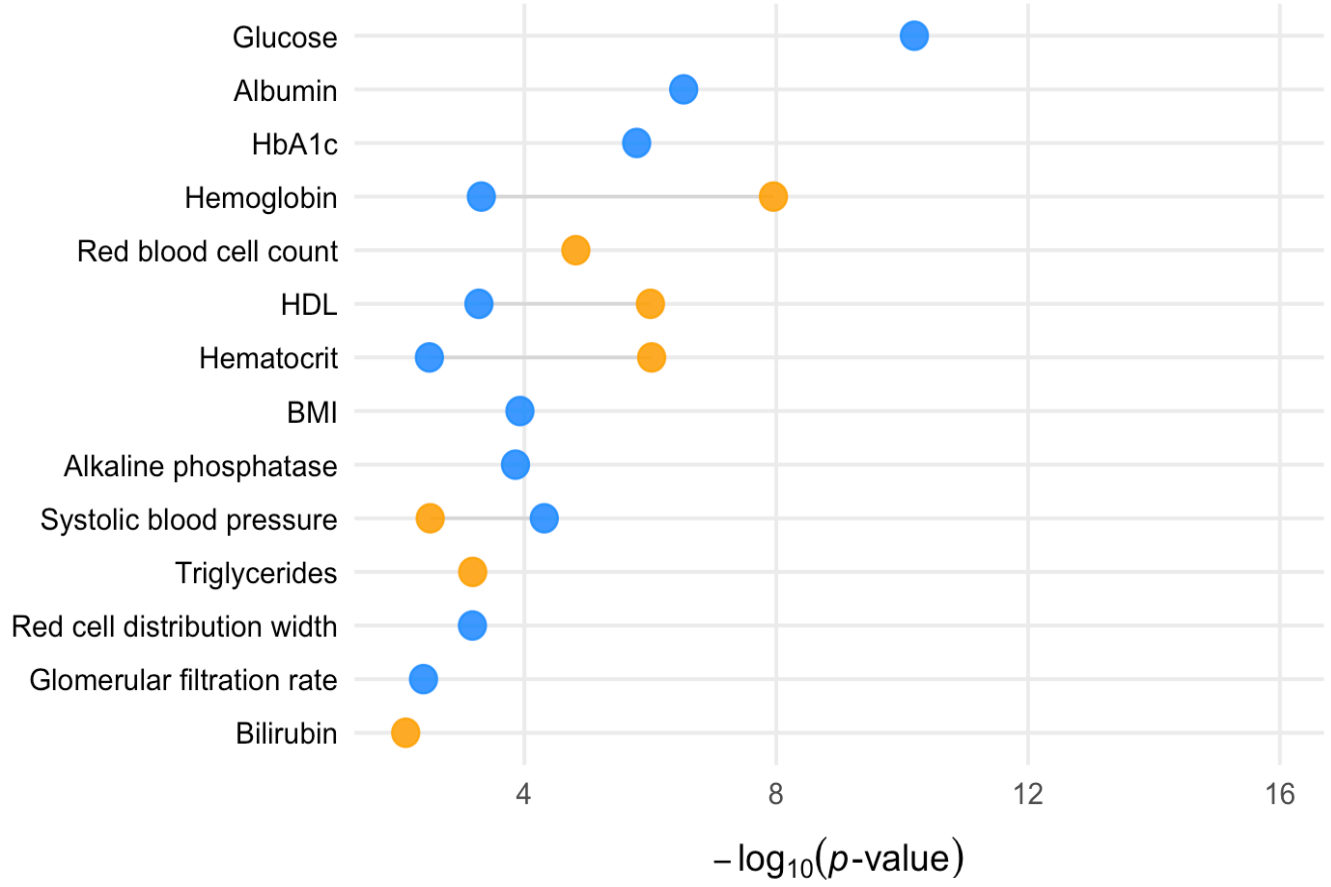


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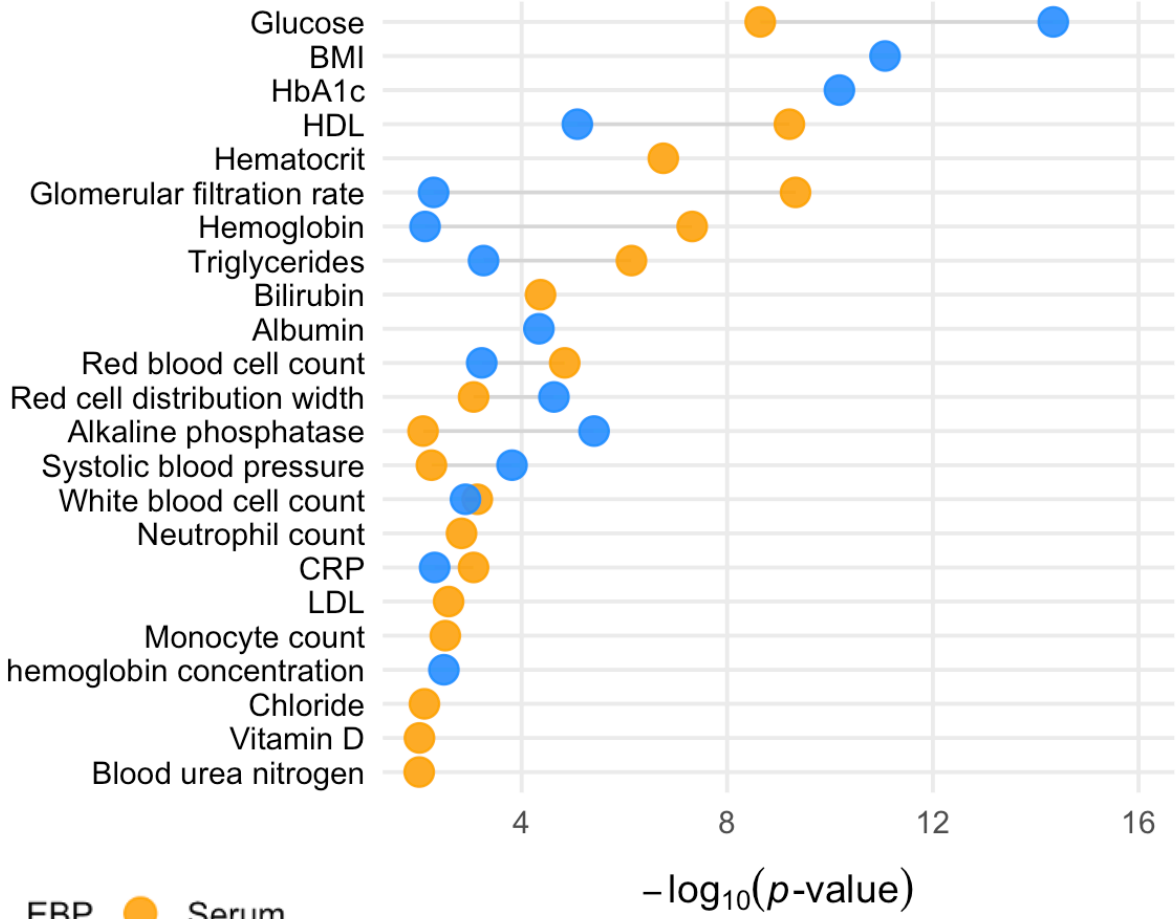
Significant EBP and serum mediators (HDMT)

Outcome: Number of Chronic Conditions (2020)

Exposure: Parental education

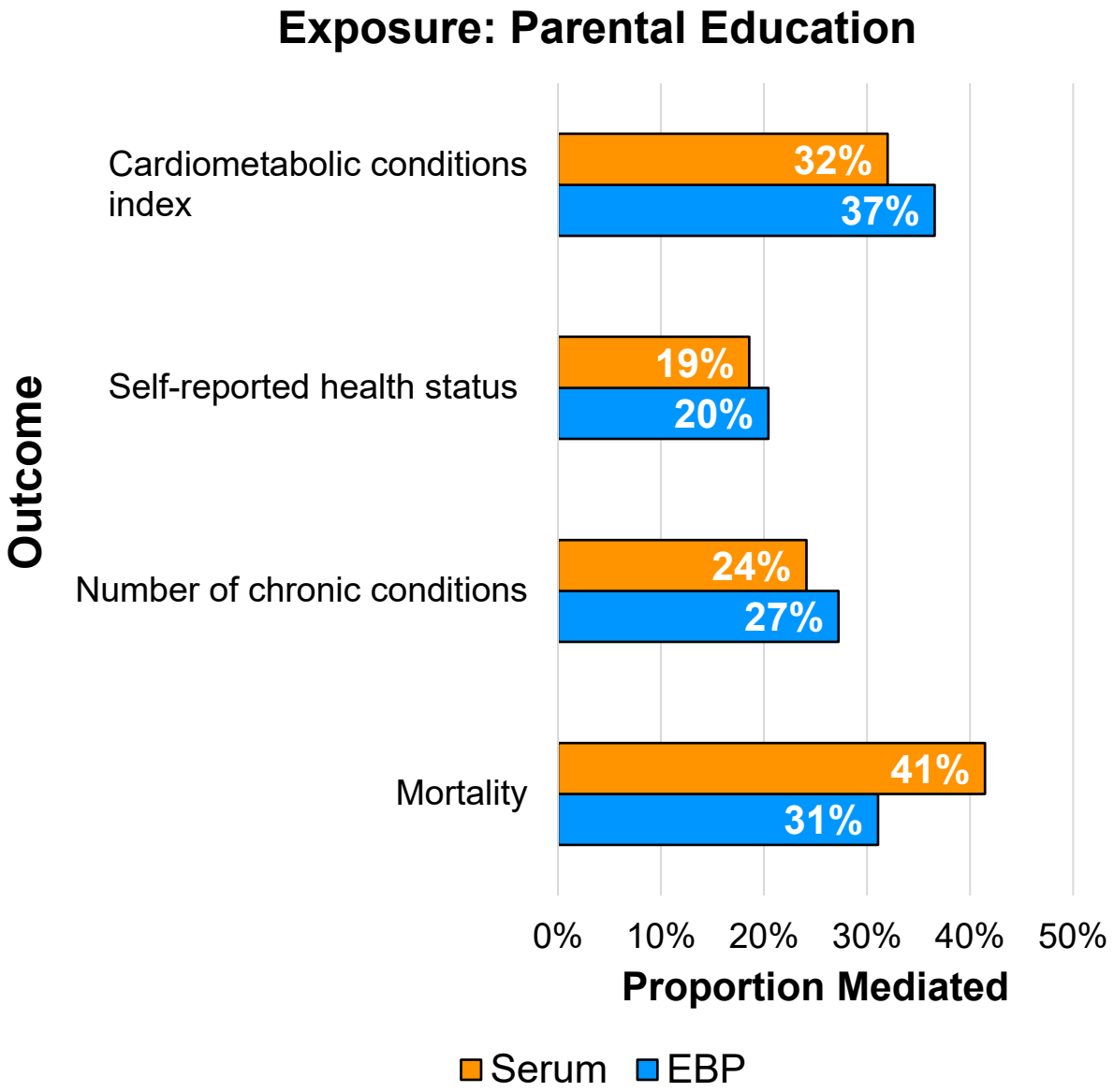


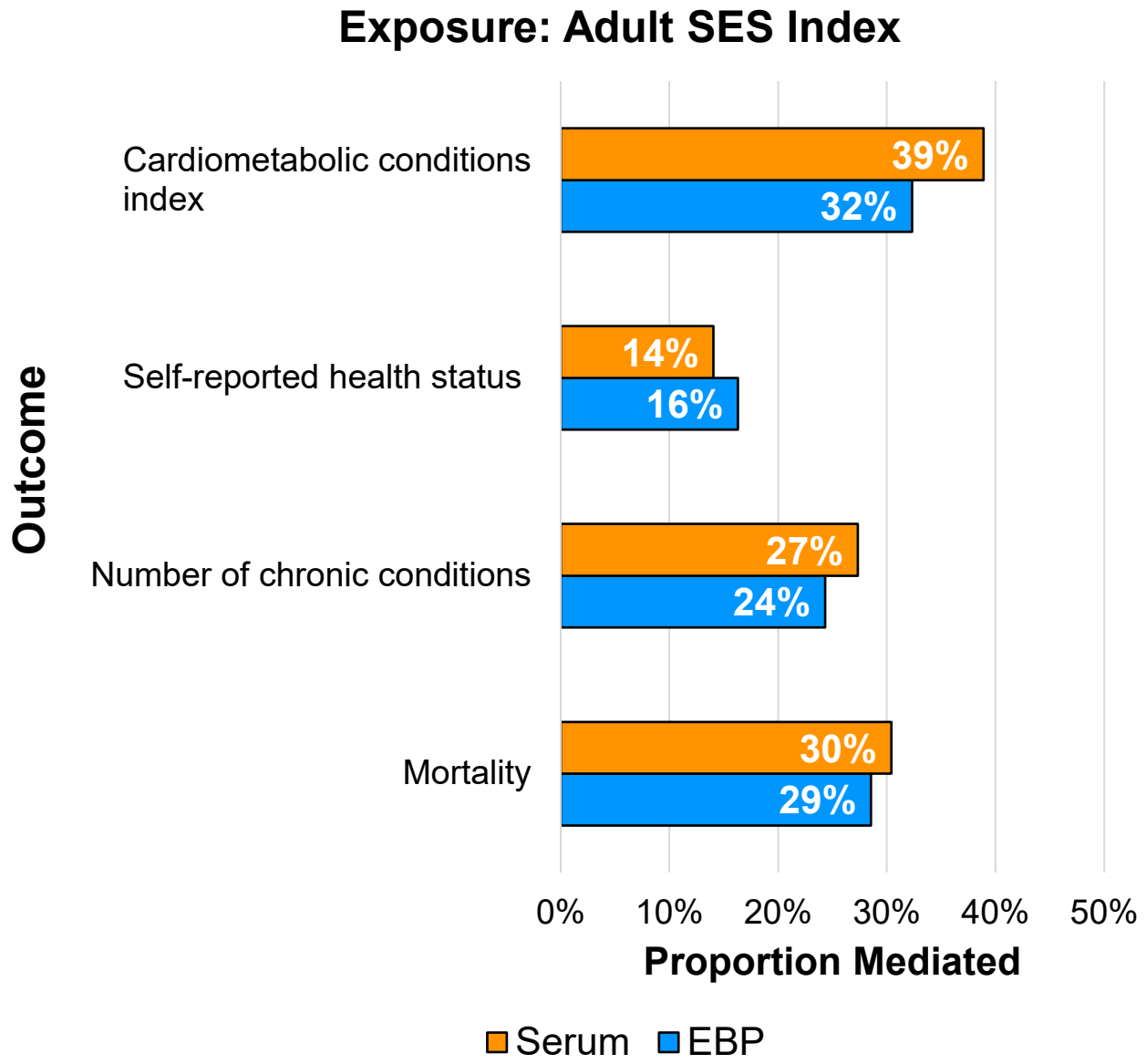
Exposure: Adult SES Index



Biomarker Source EBP Serum

Proportion mediated by serum vs. EBP biomarkers





Discussion

- We generally find higher effect sizes and lower p-values for EBPs compared to serum biomarkers for SES associations
  - Economist's take: Promising for quasi-experimental work, where more power=higher likelihood of detecting effects
- More EBPs are associated with childhood SES, whereas serum biomarkers are more associated with adult SES exposures
  - EBPs may better capture the long-arm reach of early-life exposures
  - Need better childhood SES measures and/or causal methods to test robustly
  - Replicate in younger, healthier cohorts (prior to phenotypic aging symptoms)
- Mediation results: Suggest EBPs may be more effective for exploring mechanisms linking early-life exposures to the aging process

Thank you!

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NHLBI R01 HL141292 (Smith)



BIOSOCIAL EQUITY LAB

Investigating health across the lifecourse