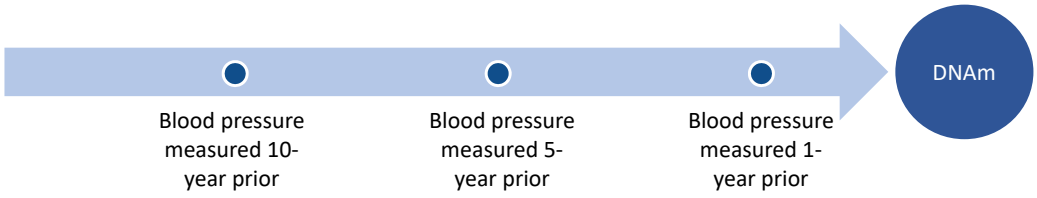
Structured Life Course Modeling Approach (SLCMA) application in the Health and Retirement Study

Farah Ammous, PhD MPH
Institute for Social Research

Biomarker Meeting 2024
Columbus OH, April 17, 2024

Rationale

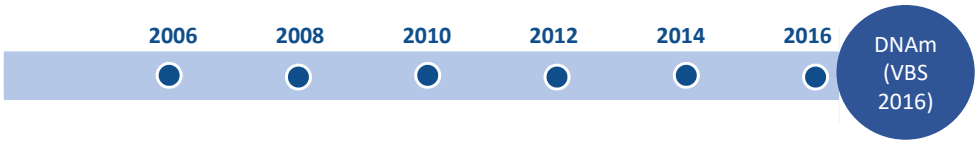
- Investigate **when** and **how** an exposure can influence DNA methylation
  - Most epigenome-wide association studies (EWAS) using a single timepoint of exposure
  - Leverage longitudinal/repeated data in panel studies
  - Important for traits like blood pressure and body mass index
- SLCMA is an efficient framework to compare life-course theories
  - Time since exposure in lieu of sensitive periods



Data and Methods

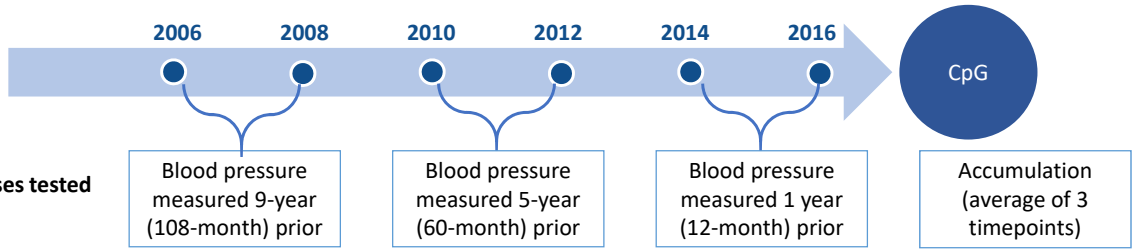
HRS HEALTH AND RETIREMENT STUDY

- Longitudinal panel study started in 1992
  - Surveys ~ 20,000 participants over the age of 50 every two years
  - Face-to-face interviews for half the sample every two years starting 2006
  - DNA methylation using EPIC microarray (Venous Blood Study in 2016)



Data and Methods

- Blood pressure traits
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - Estimated pulse wave velocity (ePWV), derived from SBP and age
    - Measure of arterial stiffness



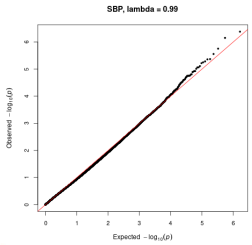
Sample characteristics

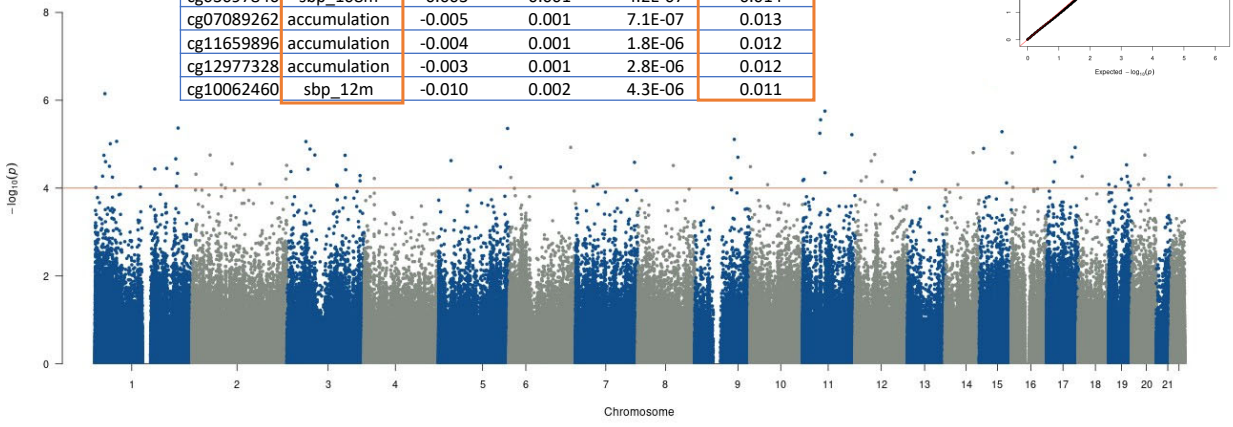
2016, N = 1,927

Variable	Mean (SD) or N (%)
Age, years	73.8 (8.4)
Female gender	1131 (56%)
Race/ethnicity	
Non-Hispanic Whites	1503 (78%)
Non-Hispanic Blacks	203 (11%)
Hispanics	177 (9%)
Other	44 (2%)
Current smoker	156 (8%)

SLCMA results for SBP

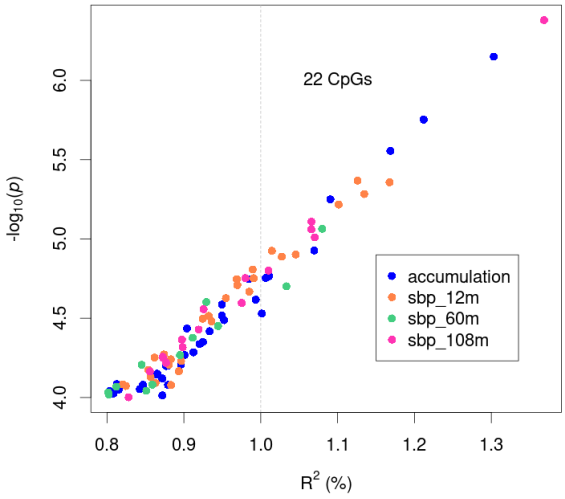
Probe	Hypothesis	Beta	SE	P-value	R^2
cg03097846	sbp_108m	-0.003	0.001	4.2E-07	0.014
cg07089262	accumulation	-0.005	0.001	7.1E-07	0.013
cg11659896	accumulation	-0.004	0.001	1.8E-06	0.012
cg12977328	accumulation	-0.003	0.001	2.8E-06	0.012
cg10062460	sbp_12m	-0.010	0.002	4.3E-06	0.011

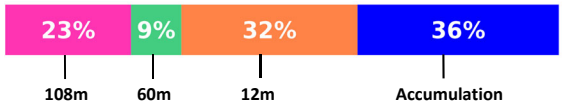




Models adjusted for age, gender, race/ethnicity, smoking, white blood cell counts

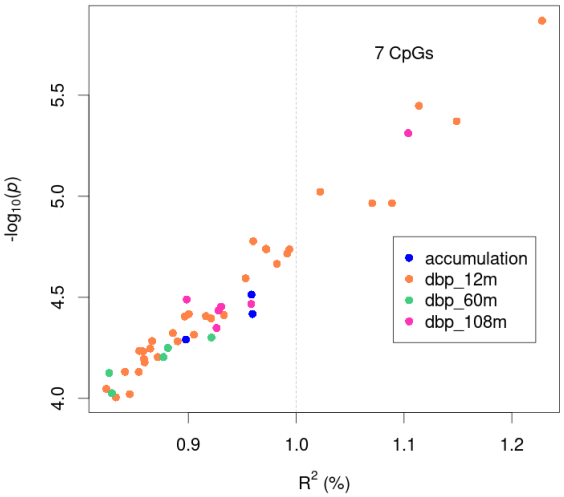
SLCMA results for SBP

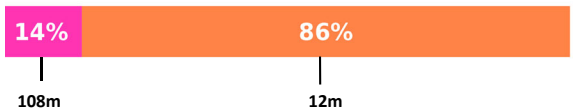




7

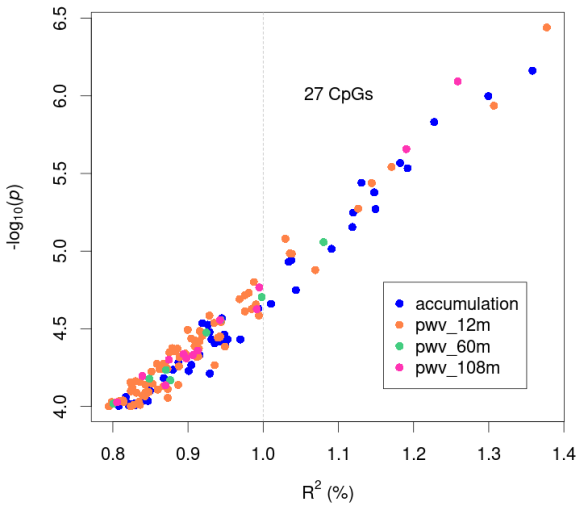
SLCMA results for DBP



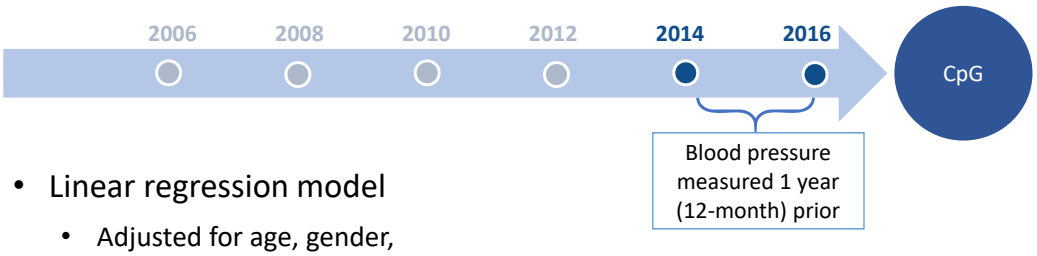


8

SLCMA results for ePWV



How does SLCMA compare to a cross-sectional EWAS?



- Linear regression model
  - Adjusted for age, gender, race/ethnicity, smoking, white blood cell counts
  - Limit sample size to the SLCMA models

Number of CpGs (P value < 10^{-4})

Exposure	SLCMA	Traditional EWAS
SBP	90	93
DBP	47	87
ePWV	150	335

Comparing SLCMA and traditional EWAS results for SBP

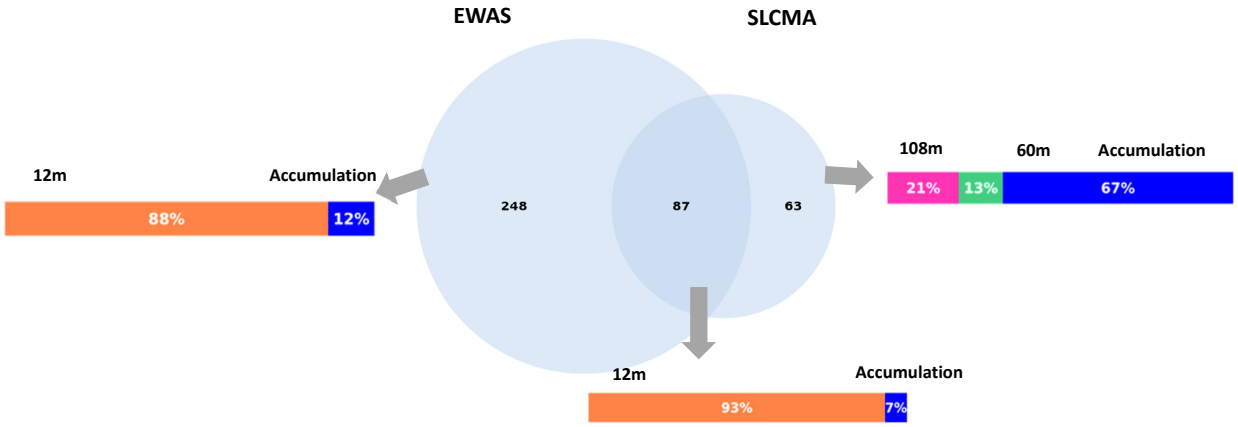
For CpGs with P < 10^{-4} in either analysis

Comparing SLCMA and traditional EWAS results for DBP

For CpGs with P < 10^{-4} in either analysis

Comparing SLCMA and traditional EWAS results for ePWV

For CpGs with $P < 10^{-4}$ in either analysis



Summary

- Provides a systematic and efficient framework for examining exposures within an aging cohort
- Identifies novel CpGs associated with accumulation/more distant exposures
- Trait enrichment analysis reveals overlap with traits like waist to hip ratio, blood pressure, and mortality
- **Limitations**
  - sample size, account for survey design/random effects, time-varying confounding
- **Future directions**
  - Investigate joint hypotheses for most significant CpGs
  - Additional annotation analysis related to biological function
  - Filter non-varying CpGs

Thank you!

fammous@umich.edu