The biological influences of social determinants of health: challenges, surprises and complexities

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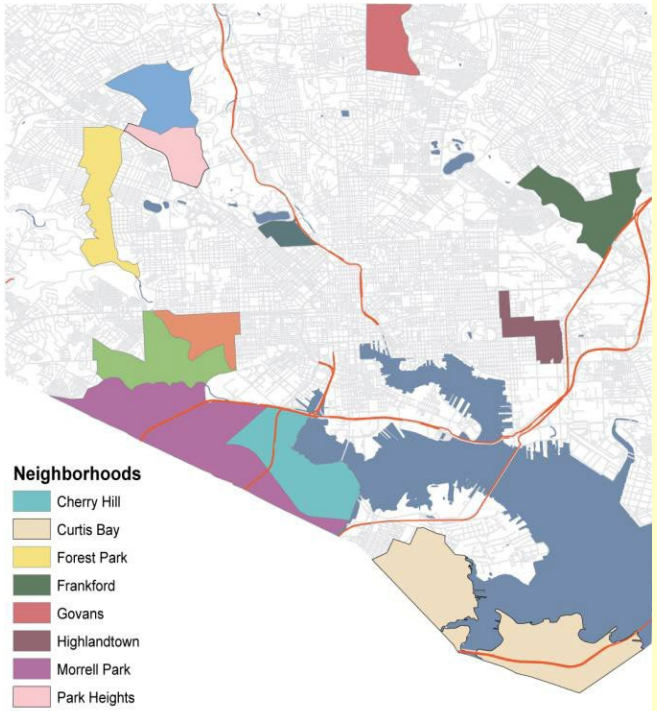
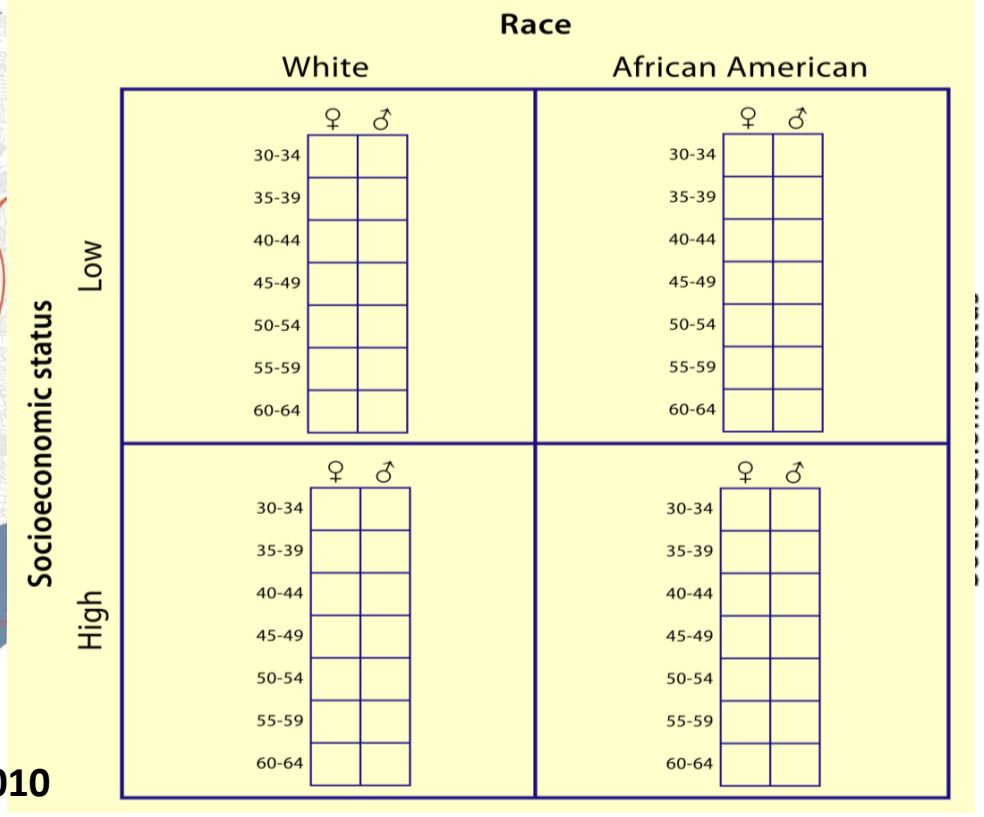
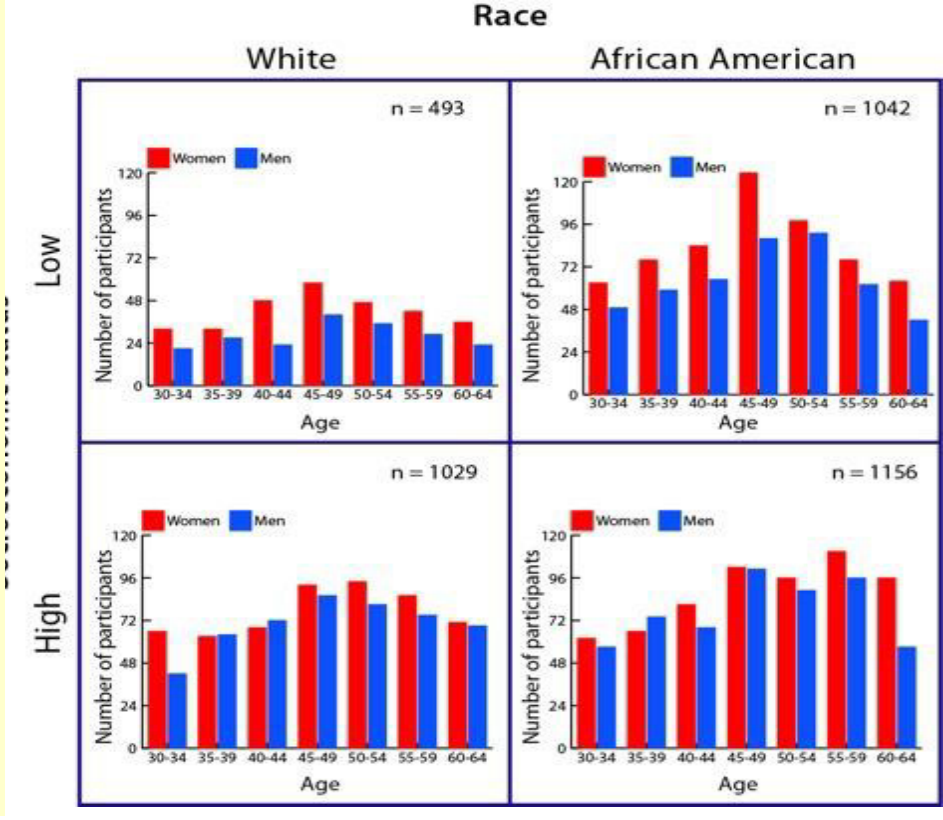
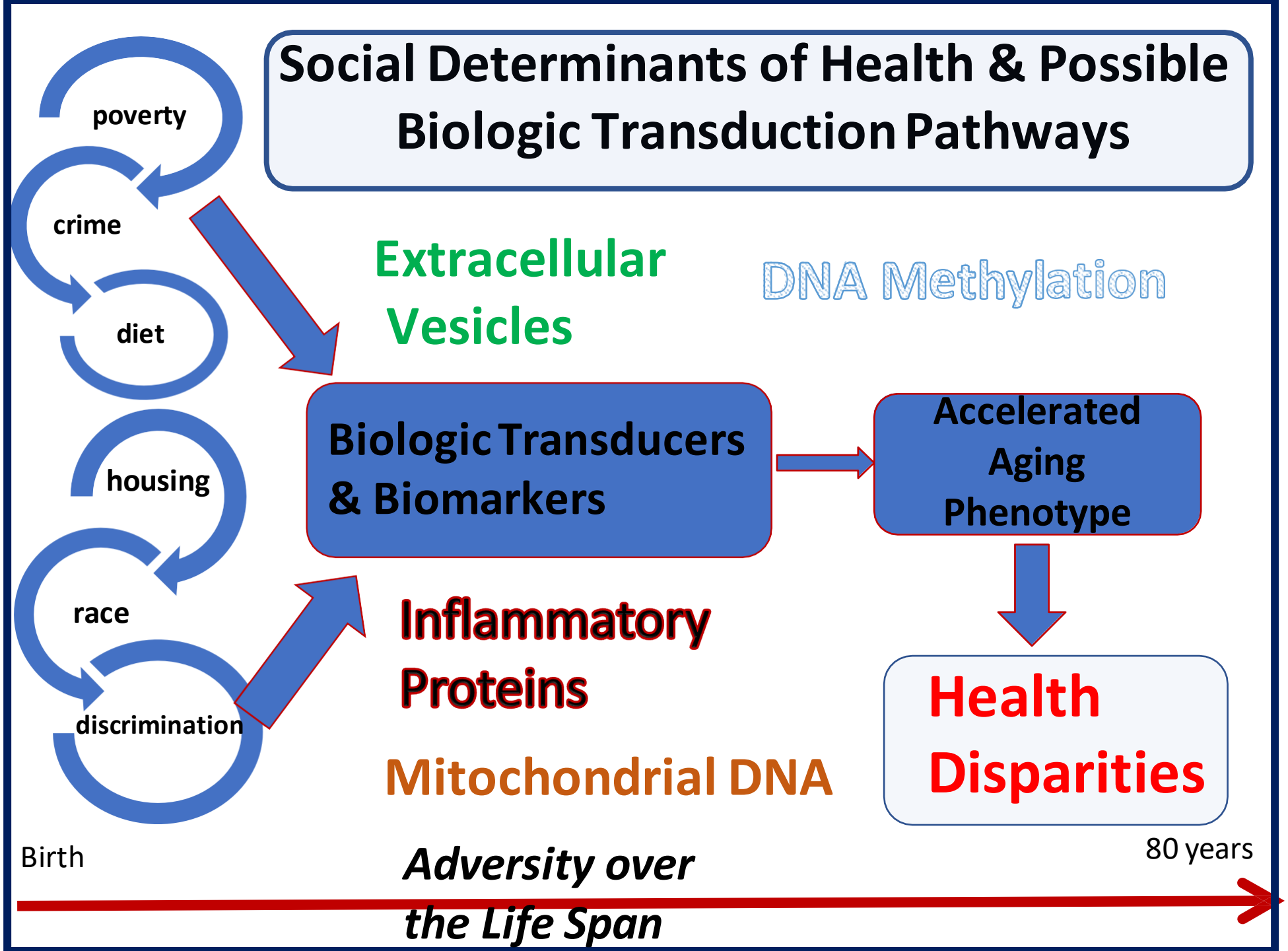


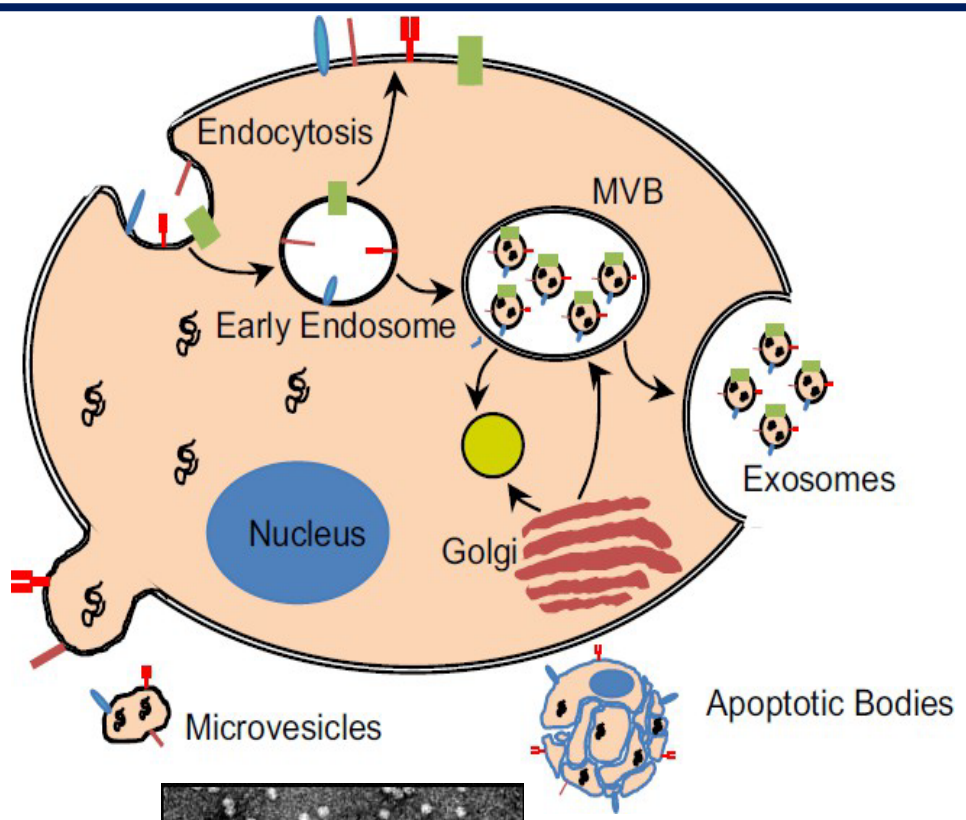
Evans MK et al *Ethn. Dis.* 2010

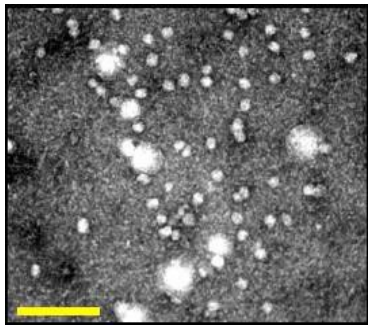





Social Determinants of Health & Possible Biologic Transduction Pathways
poverty
crime
diet
housing
race
discrimination
Extracellular Vesicles
DNA Methylation
Biologic Transducers & Biomarkers
Accelerated Aging Phenotype
Inflammatory Proteins
Mitochondrial DNA
Health Disparities
Birth
80 years
Adversity over the Life Span

Extracellular Vesicles as Biomarkers of Health Disparities

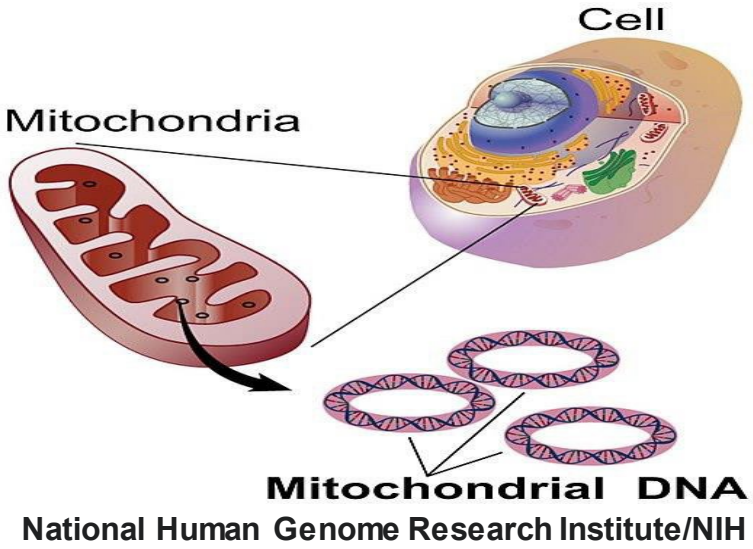




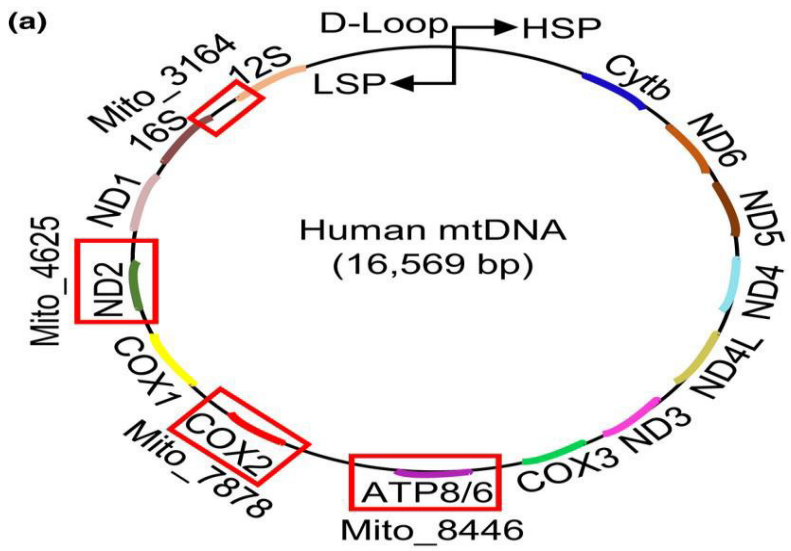
Noren Hooten N & Evans MK 2020

- Cells release lipid-bound extracellular vesicles (EVs): exosomes, microvesicles and apoptotic bodies into the extracellular space e.g. plasma, serum, urine
- Mediate intercellular communication
- Biomarkers and novel therapeutic modalities for chronic disease & cancer
- Contain molecular cargo, including RNAs (mRNA, microRNAs, and long noncoding RNAs), DNA, proteins, and lipids

Circulating Cell Free Mitochondrial DNA as biomarkers of health disparities



National Human Genome Research Institute/NIH



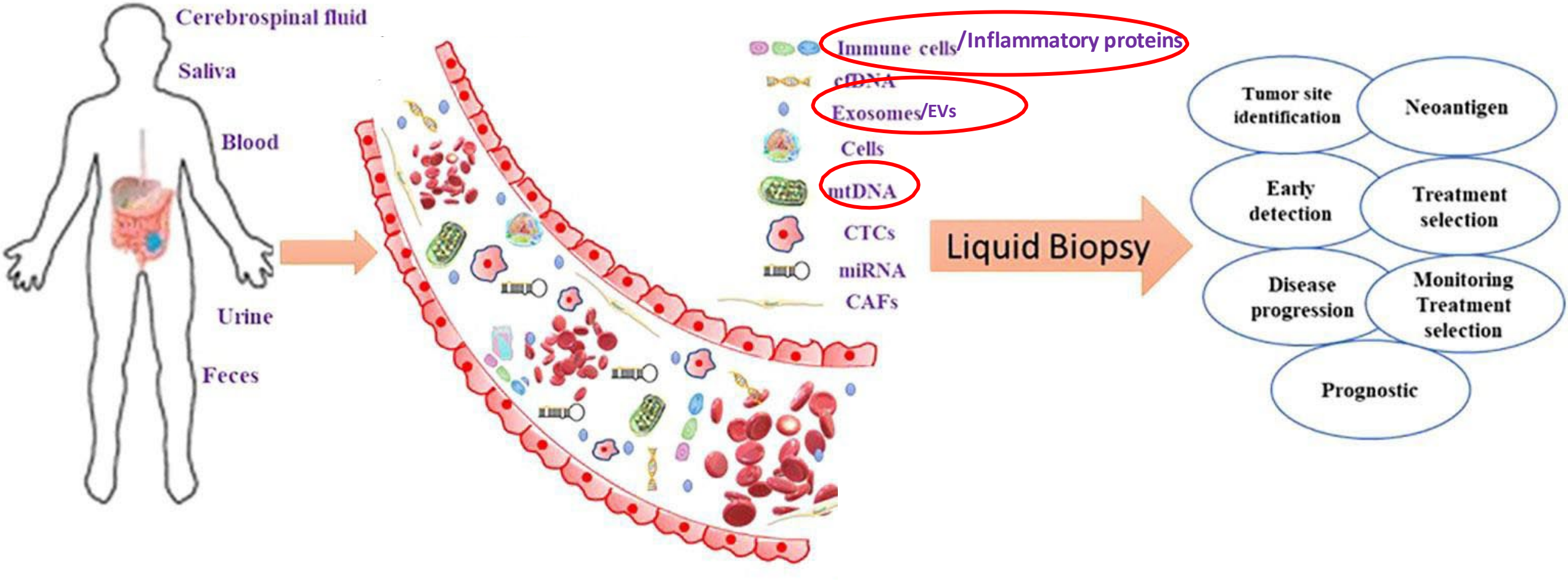

S Lazo


J Green


N Noren Hooten

- Released from cells under stress
- Mt and mtDNA may be mediators of stress relevant to SDOH
- Damage-associated molecular pattern molecules (DAMPs) associated with cancer and chronic inflammatory diseases
- Plasma mtDNA is present in EVs, EV-derived mtDNA declines with age, EVs affect mitochondrial energetics in an EV age-dependent manner. Lazo S, Noren Hooten N, Green J *Aging Cell* et al 2021

Liquid Biopsy in Cancer



Do social determinants of health influence liquid biopsy molecular and clinical assessments?

modified from Mirza S et al *Front. Oncol.* 2023

EVs, Inflammation, Poverty


A. Byppanahalli


M. Vannoy

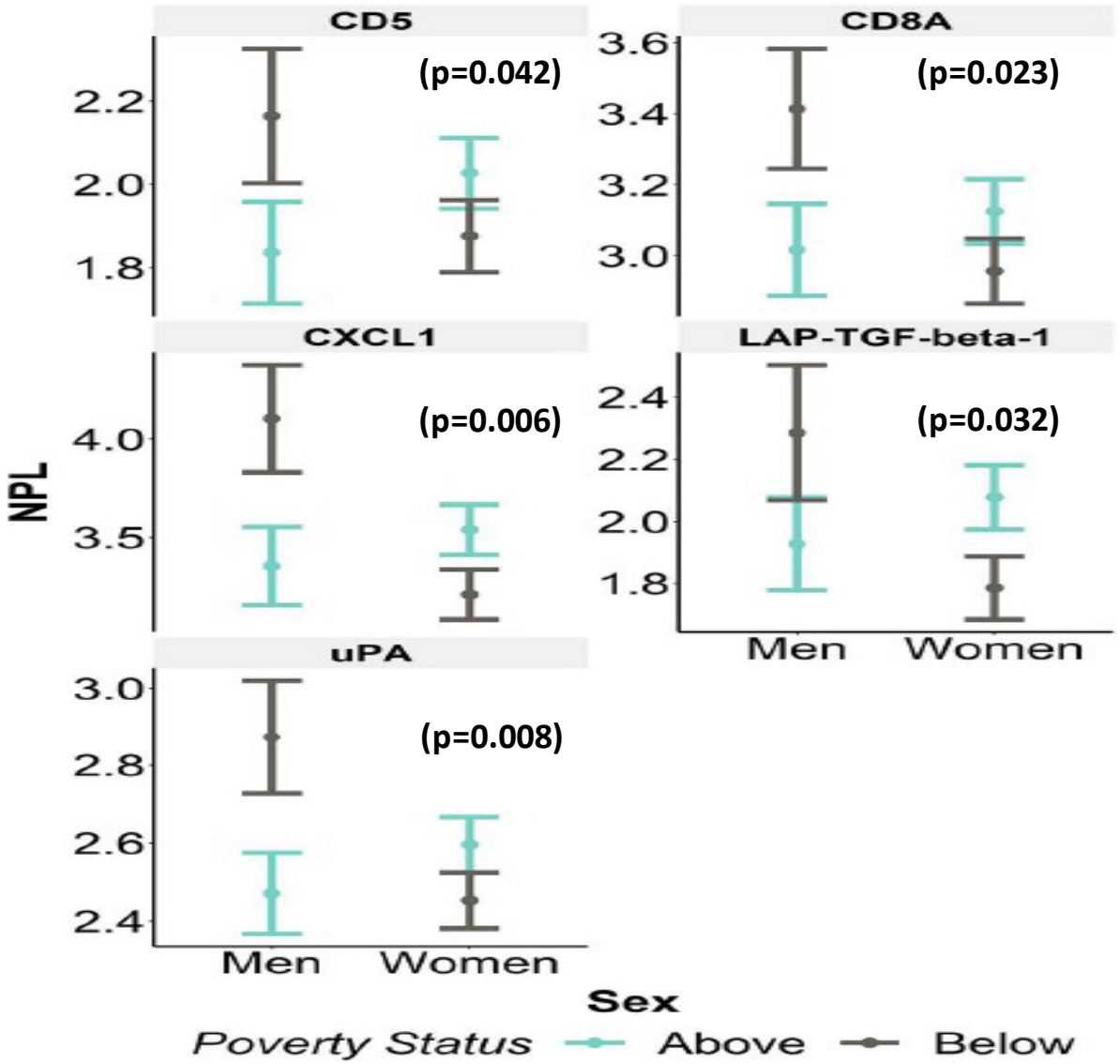

N. Noren Hooten

- We examined whether mitochondrial DNA (mtDNA) and inflammatory proteins in EVs may act as damage-associated molecular pattern (DAMP) molecules in frailty in the context of race, age and poverty status.

Characteristic	Frail, *N* = 87	Non-frail, *N* = 90	***P*-value**
Age	50.66 (2.62)	50.06 (2.84)	0.15
Men (%)	24 (28%)	25 (28%)	> 0.9
AA (%)	41 (47%)	43 (48%)	> 0.9
Below Poverty (%)	43 (49%)	38 (42%)	0.3

Byppanahalli AM, Noren Hooten N, Vannoy M et al *Immunity & Aging* 2023

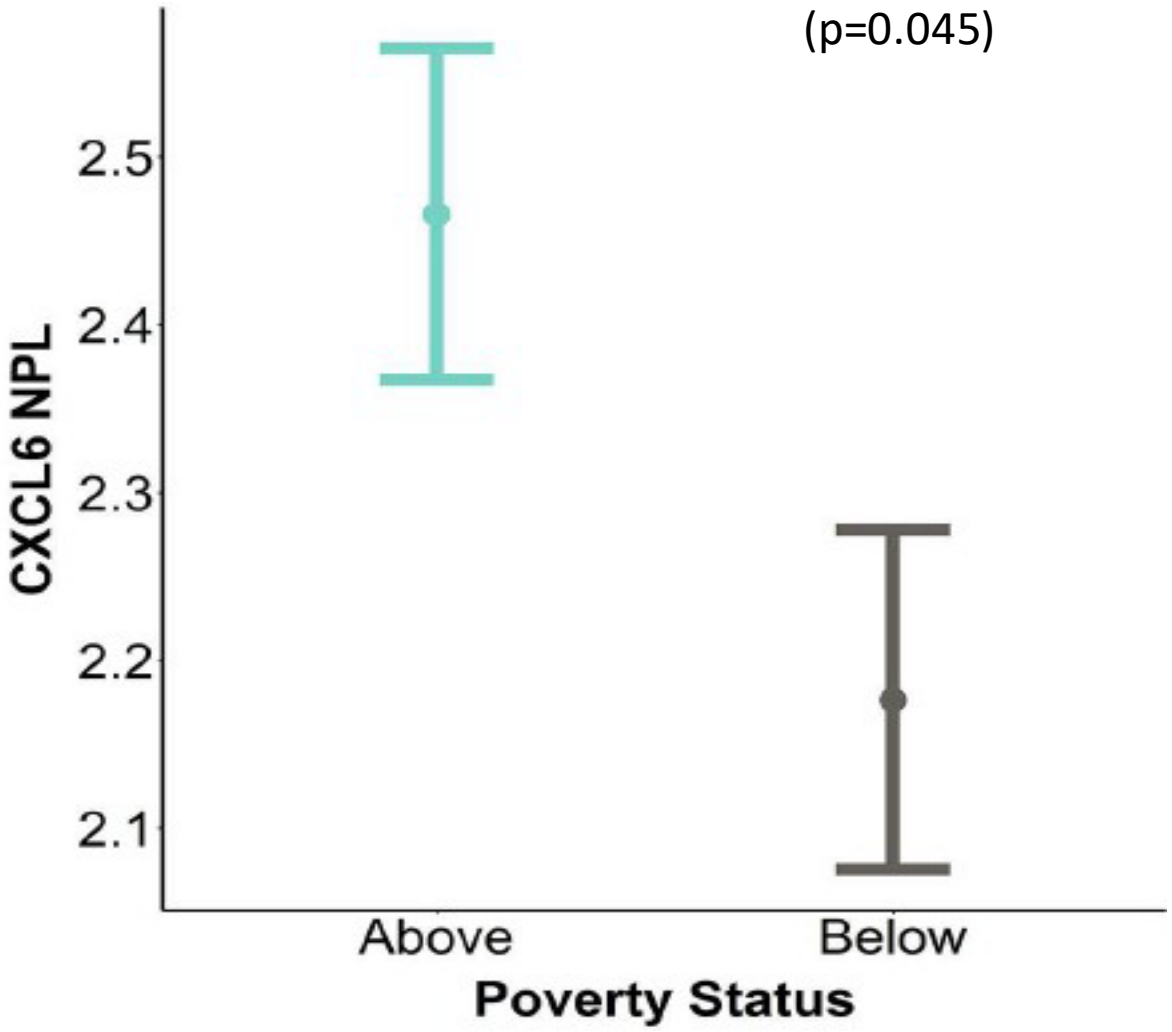
EV inflammatory proteins are associated with sex and poverty status



- 5 proteins significant interactions between sex and poverty status
- All 5 proteins highest in men **below poverty**
- All proteins except **CD5** *(regulates antitumor immune response)* higher levels in men **below poverty** compared to women below poverty
- **CXCL1** *(role in inflammation, angiogenesis, tumorigenesis)* **and uPA** *(involved in cancer progression and tumor microenvironment remodeling)* - higher in men **below poverty** compared to men **above poverty**
- **LAP-TGF-beta-1** *(cytokine regulates cellular proliferation and differentiation)* - lower in women **below poverty** compared to women **above poverty**

Byppanahalli AM, Noren Hooten N, Vannoy M et al *Immunity & Aging* 2023

CXCL6 levels were significantly different with poverty status



- **C-X-C motif chemokine ligand 6** (CXCL6) chemotactic for neutrophil granulocytes
- mediates inflammation, cell growth, promotes tumor growth, and metastasis,
- CXCL6 lower in individuals **below poverty** compared to **above poverty**

Byppanahalli AM, Noren Hooten N, Vannoy M et al *Immunity & Aging* 2023

EV inflammatory proteins significantly altered by frailty status,sex, and poverty status

- Evs & EV mtDNA levels were significantly higher in frail individuals compared to non-frail individuals
- Five proteins had significant interactions between sex and poverty status: CD5, CD8A, CXCL1, LAP-TGF-β1, Urokinase Type Plasminogen activator- *immune response, inflammation, cancer*
- In general, all five proteins were highest in men living below poverty
- CXCL6 levels were significantly different with poverty status

Does race associate with EVs, cell free circulating mtDNA or inflammatory protein levels?

Byppanahalli AM, Noren Hooten N, Vannoy M et al *Immunity & Aging* 2023

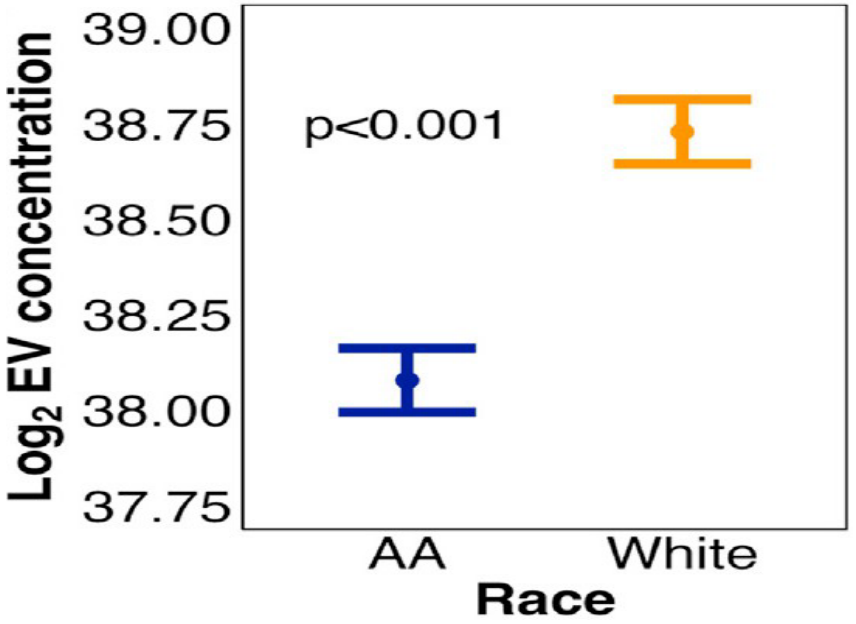
Race, EVs, mtDNA, & inflammatory proteins


A. Byppanahalli


V. Omoniyi


N. Noren Hooten

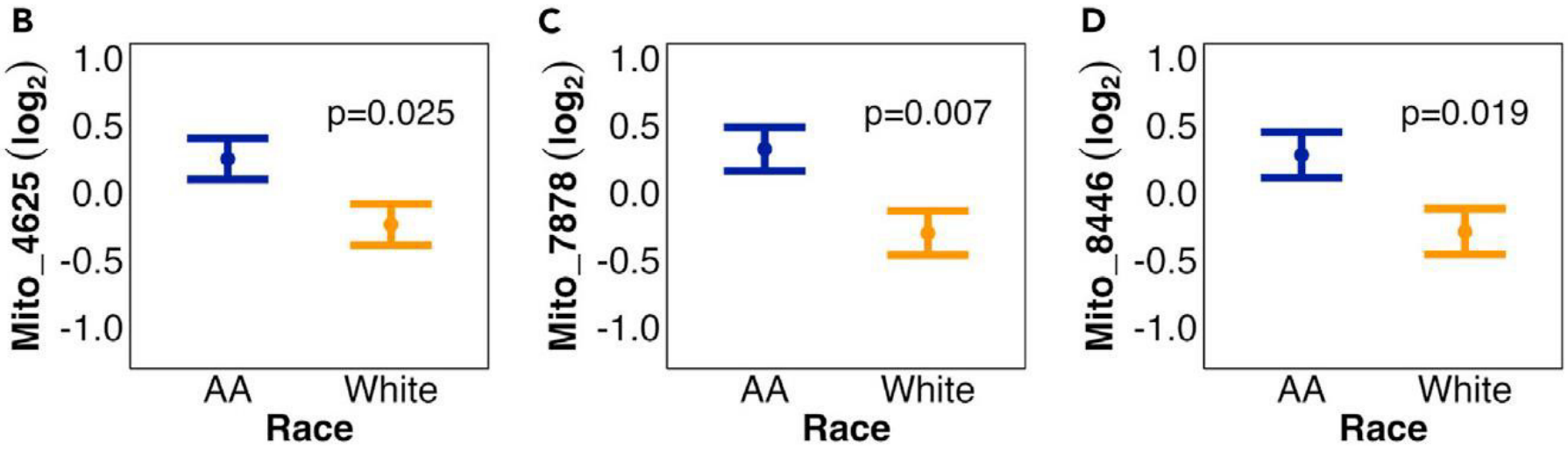
Characteristic	NT, N = 107	HTN, N = 108	p value
Age	52.6 (4.3)	53.1 (4.1)	0.3
AA (%)	54 (50%)	54 (50%)	>0.9
Men (%)	54 (50%)	54 (50%)	>0.9
Below poverty (%)	46 (43%)	47 (44%)	>0.9



EV concentration was significantly higher in White participants compared with African American participants ($p < 0.001$)

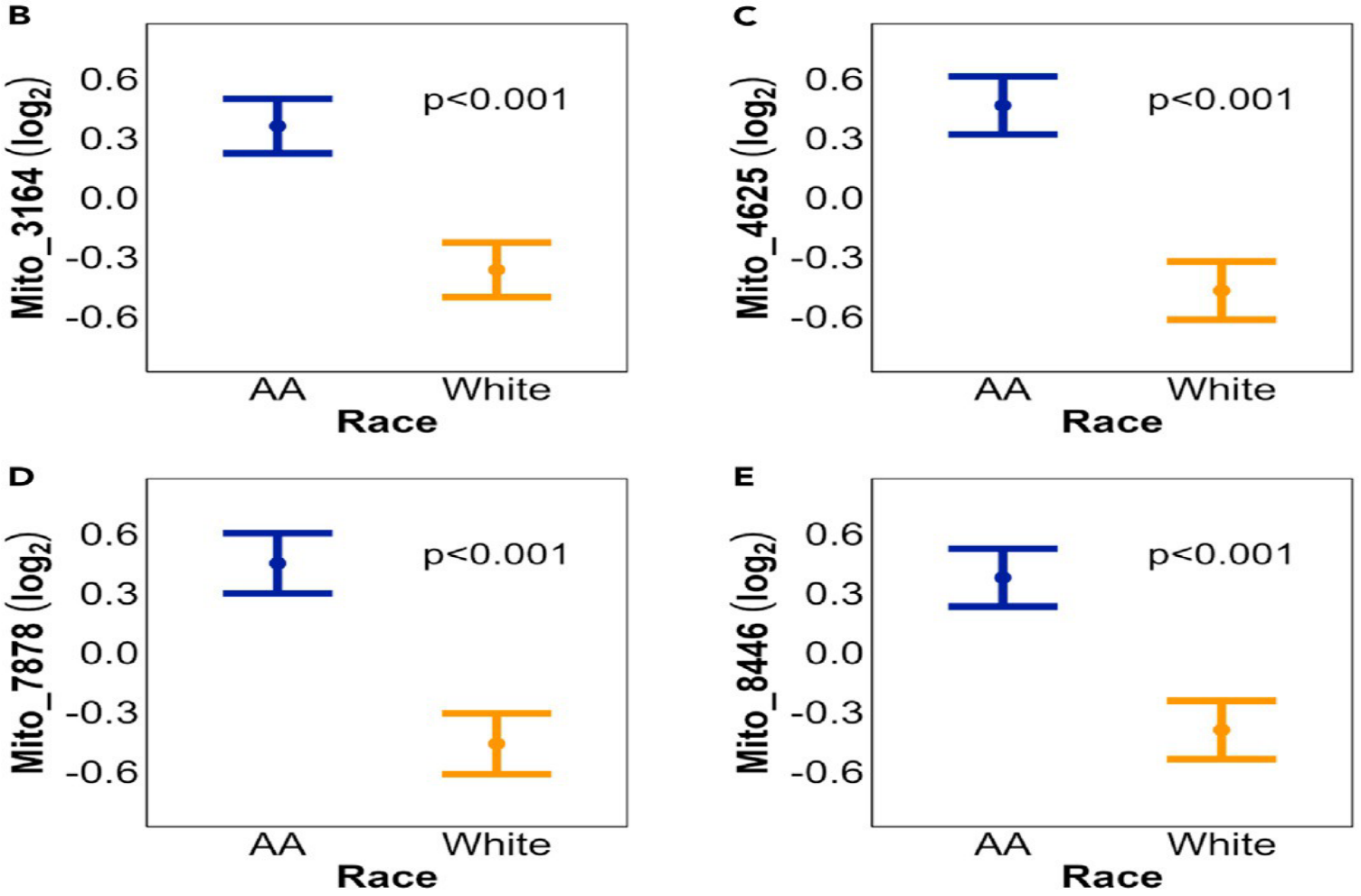
Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

Plasma mtDNA levels are significantly higher in African American participants



Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

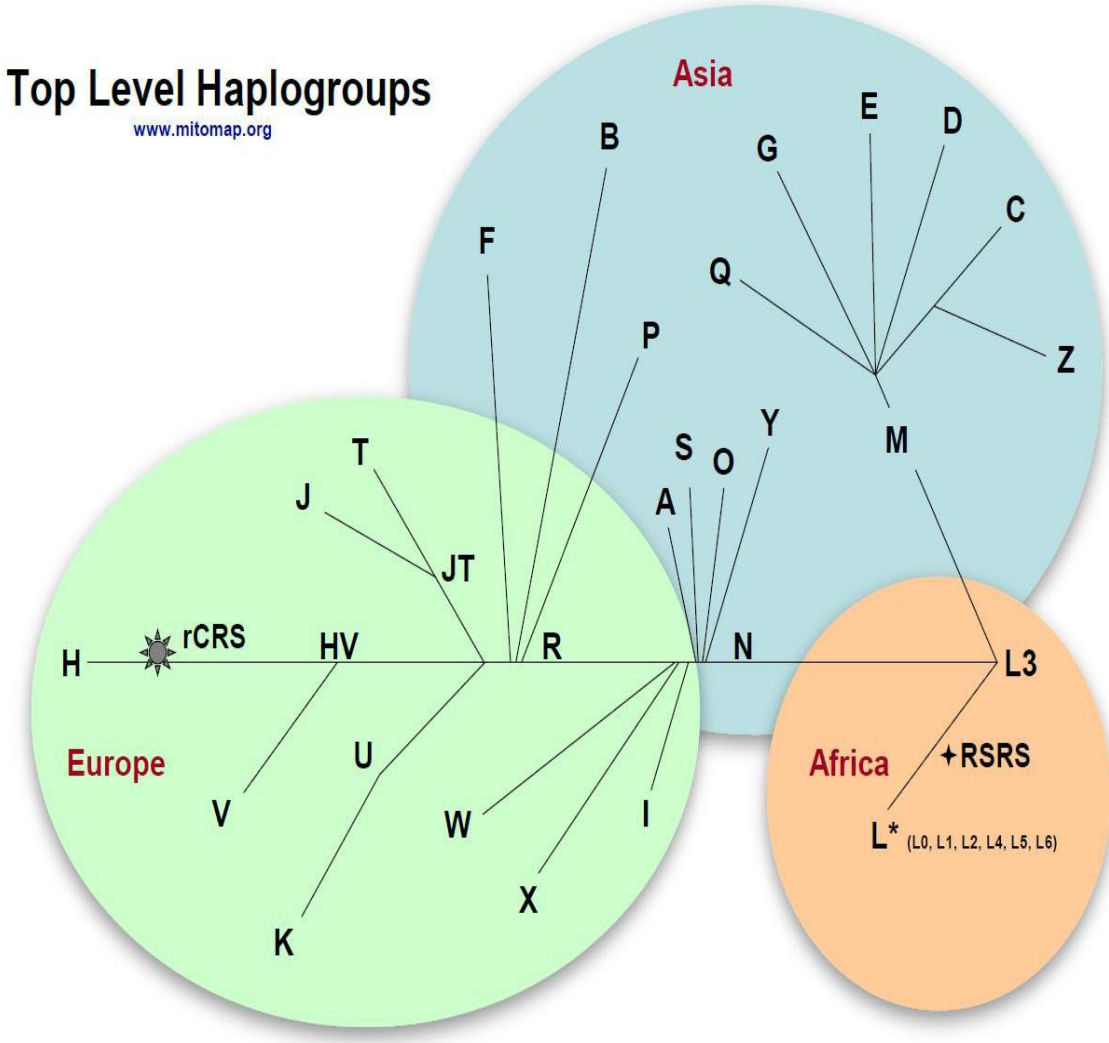
EV mtDNA levels are higher in African American participants



Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

Race is a social construct

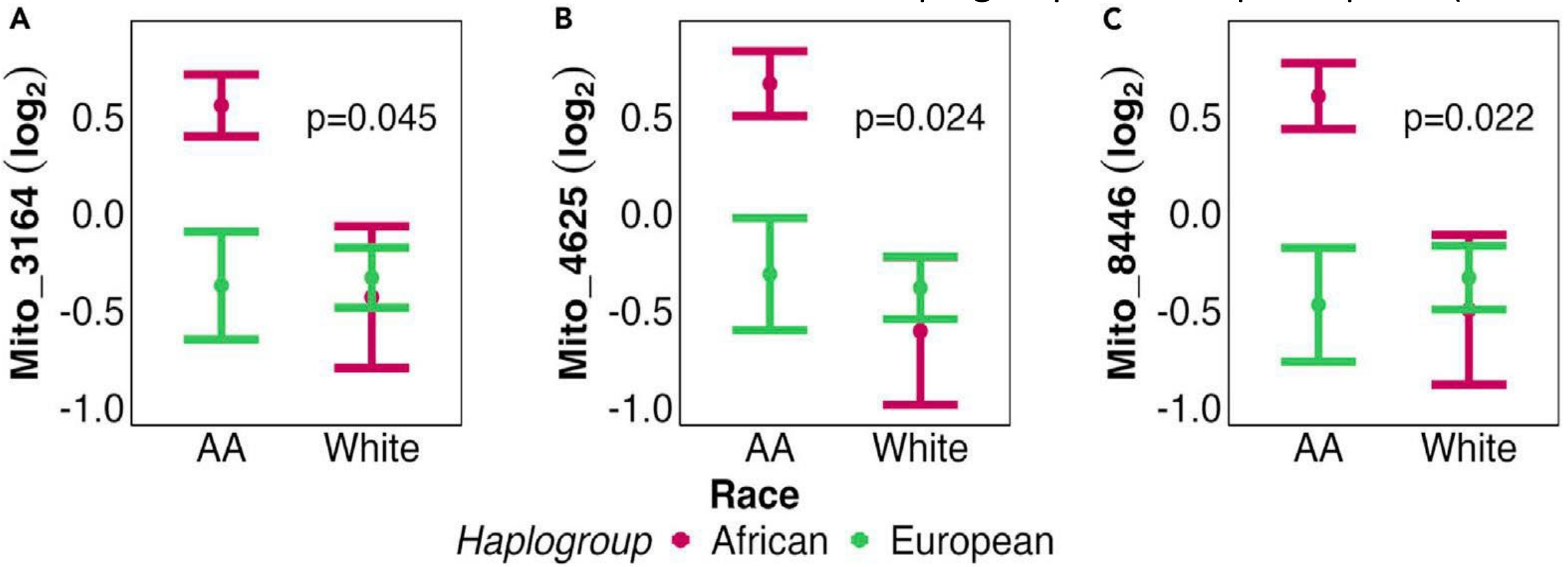
- "**Race is meaningful for health-** a *risk factor* for poor health outcomes in the context of social status, access to resources, *ancestry, genomic variation*" – (Moring A 2020)
- Mitochondrial haplogroups - genetic classifications within a population, defined by shared, inherited genetic markers or mutations - similar haplotypes defined by combinations of single nuclear polymorphisms (SNPs) in mtDNA inherited from a common ancestor. (Wallace D 2012)
- mtDNA haplogroups - mitochondrial function, mtDNA damage, oxidative phosphorylation efficiency, ROS production, disease risk including cancer (Wallace DC 2013)



www.mitomap.org

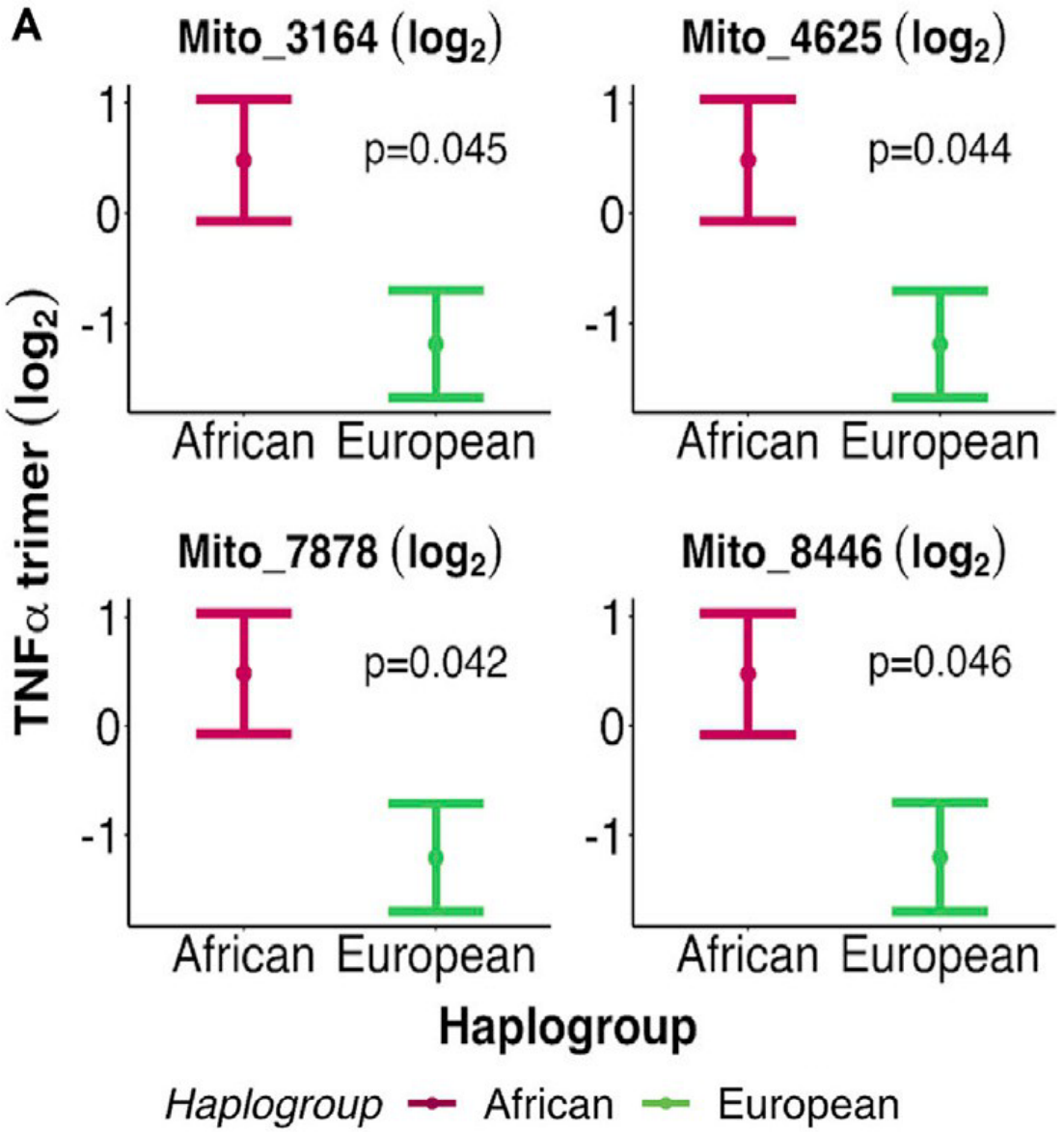
Higher EV mtDNA in African American participants with the African haplogroup

- Participants were grouped into mtDNA haplogroups: African (L0, 1, 2, 4, 5, 6, and L3), European (H, HV, J, K, T, U, and UK), and Other (B-P-F-R, M, and N-A-Y-W-I-X).
- There was concordance between race and mtDNA haplogroup for most participants (AAs 72%)



Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

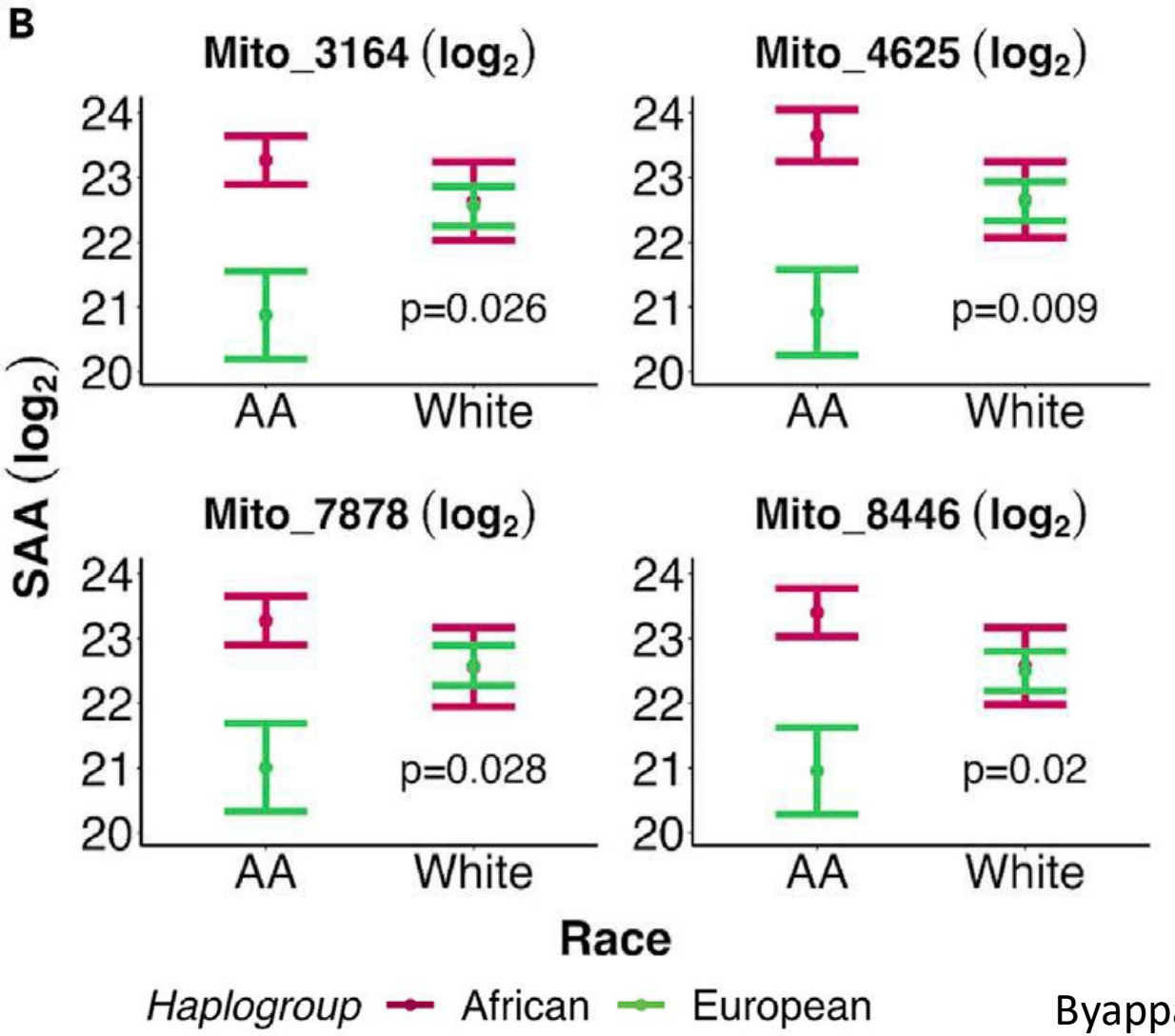
Inflammatory protein levels are associated with mitochondrial DNA haplogroup, race, and EV mtDNA



- Nine serum inflammatory proteins were assayed
- Linear regression used to analyze the relationship between each inflammatory protein, race, each EV mtDNA region, and mtDNA haplogroup.
- **TNF-a** – pro-inflammatory cytokine associated with cancer progression and treatment
- **TNF-a trimer levels** significantly different with haplogroup for each EV mtDNA region studied
- **TNF-a Levels were higher in those with African mt Haplogroups.**

Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

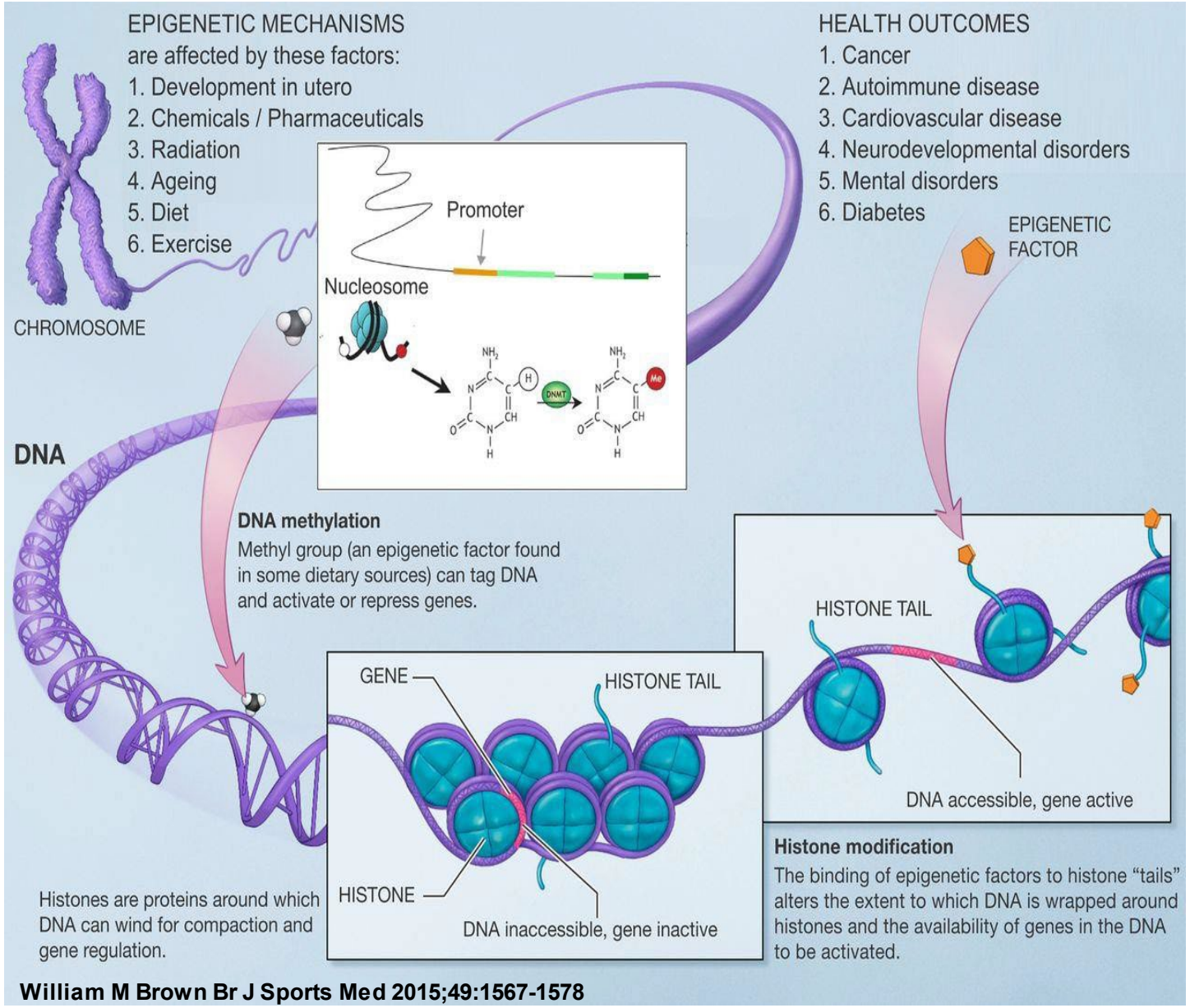
Inflammatory protein levels are associated with mitochondrial DNA haplogroup, race, and EV mtDNA



- **Serum Amyloid A (SAA)**
- Acute phase protein secreted by cancer cells
- Cytokine-like protein involved in cell-cell communication, inflammation and neoplasia
- SAA levels significantly different with haplogroup and race for each EV mtDNA region

Byappanahalli AM, Omoniyi V, Noren Hooten N et al *iScience* 27; 2024

Race & Poverty: DNA methylation & Biological Aging



William M Brown Br J Sports Med 2015;49:1567-1578

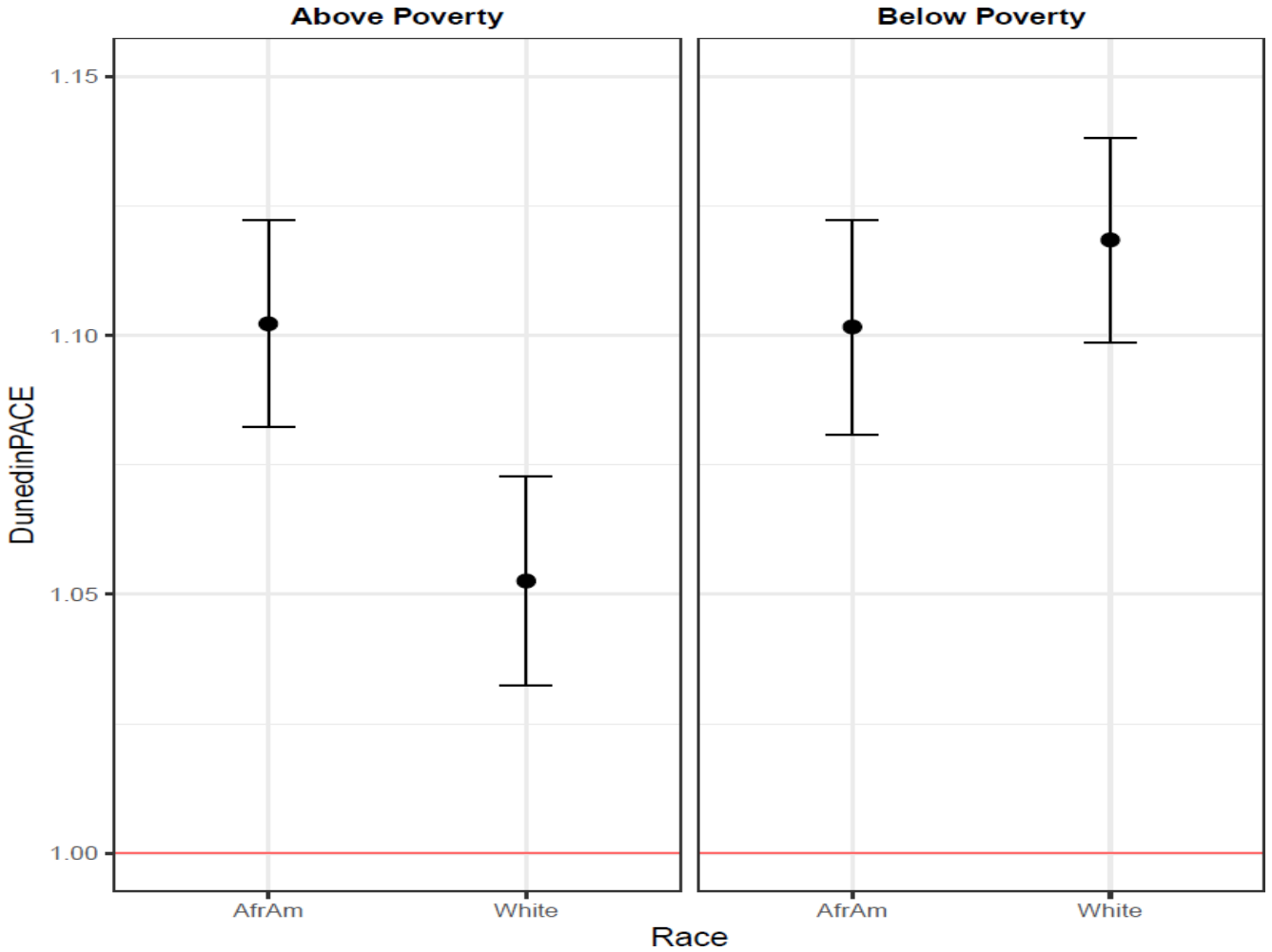
- DNA methylation (DNAm) is the most understood epigenetic marker.
- Hypermethylation generally triggers gene expression silencing, while the reverse is true for hypomethylation
- Epigenetic modifications are closely linked with aging & cancer
- Biological aging - changes over the lifespan in pathophysiologic and organismal function
- 'Slow agers' are those who maintain a 'healthy' phenotype despite advancing age
- 'Fast agers' develop age-associated disease earlier in the life span
- Biological age prediction algorithms based on DNAm at selected CpG sites = 'epigenetic age'
- Difference in epigenetic and chronological age - 'epigenetic age acceleration' reflecting the rate of biological aging

DunedinPACE Measure

- **P**ace of **A**ging **C**omputed from the **E**pigenome -designed to measure aging.
- Detect the effects of interventions to slow aging
- Detect exposures that accelerate aging
- Tracks changes in 19 biomarkers of organ-system integrity in the 1000-member Dunedin Birth cohort in New Zealand

DunedinPACE scores are associated with race and poverty status

Botong Shen



- HANDLS participants aging 7% faster than the Dunedin Study cohort.
- Living below poverty and racial identity associated with faster biological aging
- White participants living above poverty had a DunedinPACE score near 1
- White participants' DunedinPACE scores differed based on poverty status, which was associated with faster biological aging.
- AA participants regardless of poverty status had DunedinPACE scores above one
- Unable to detect the effects of senolytics to slow aging in diverse populations

Shen B et al *JAMA Network Open* 2023