

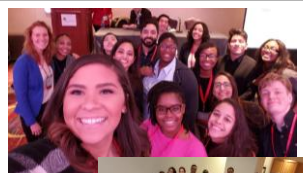
Contributions of Intergenerational Research to Understanding Mechanisms of Disparities in Alzheimer's Disease and Cognitive Aging

Presented by: Jennifer J. Manly

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Supported by

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Overview

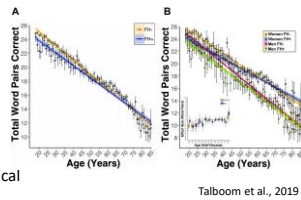
- Value of intergenerational dementia research
- Mechanisms underlying parental dementia risk
 - Accelerated biological aging
- Is family history = destiny?
- Opportunities for intervention in midlife



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Family History of Dementia

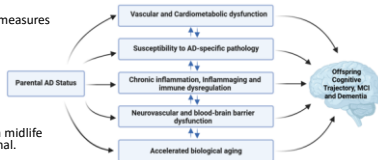
- First-degree family history increases risk of:
 - Dementia risk approximately 4-10 fold
 - Earlier dementia onset
 - Lower cognitive test performance
 - Presence of biofluidic and neuroimaging AD biomarkers, amyloid and tau pathology and cerebrovascular disease
- Risk is apparent long before clinical symptoms emerge



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Effects of Parent History of Dementia in Midlife

- Associated with:
 - Lower cognitive test performance
 - Evidence of more rapid cognitive decline
 - Greater vulnerability to brain atrophy
 - Evidence of accelerated inflammatory
 - Altered epigenetic aging measures

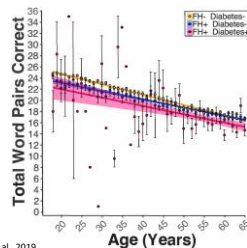


- While offspring are still in midlife and largely clinically normal.

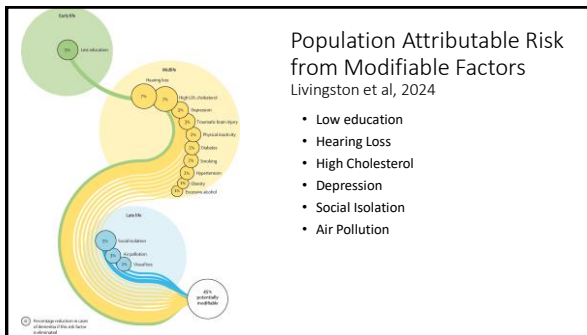
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Modifiers of Parent Dementia Risk Point toward Prevention Opportunities

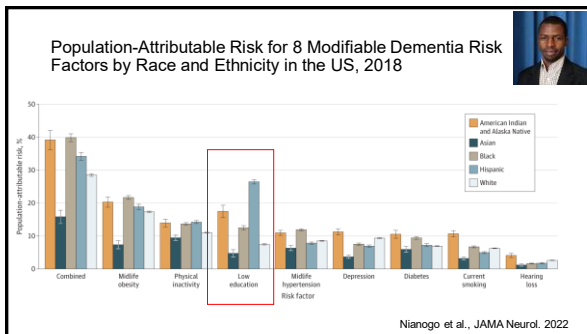
- Effects of FH vary substantially across individuals
 - Familial risk is modified by other biological and social factors.
- Parental dementia history identifies vulnerability, while life-course exposures influence whether that vulnerability is amplified or buffered
- Understanding why some individuals with parental dementia risk remain cognitively healthy may reveal promising targets for prevention



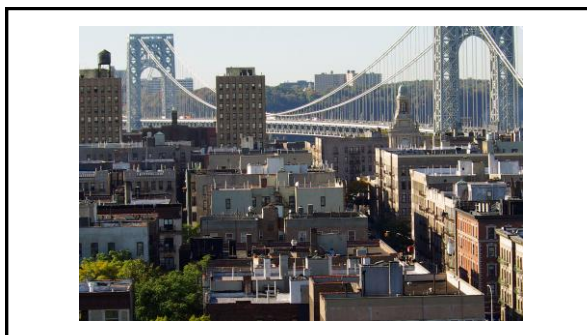
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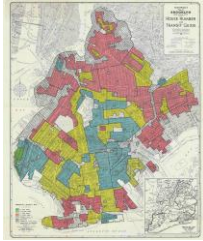
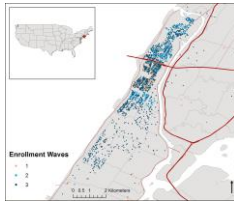


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Neighborhood context and brain health



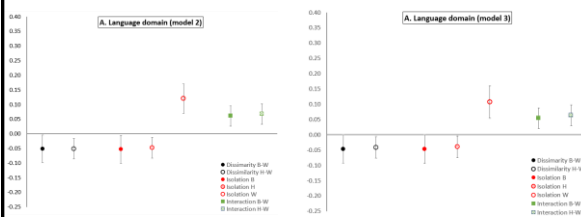
Nika Seblova



Danny Pohl

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Residential segregation & Language abilities



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WHICAP

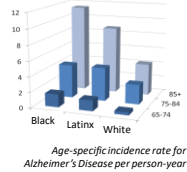
MPs: Richard Mayeux, Adam Brickman, & Jennifer Manly

- N > 6,700 older adults
- Inclusion criteria: Medicare-eligible residents, age 65+, Spanish or English speaking
- Seen in home at 18-24 month intervals
- Women (66%) outnumber men (32%), consistent with age group
- Tested in Spanish (37%) or English (63%)
- Dx based on neuropsychological test battery, medical & functional interview

Offspring

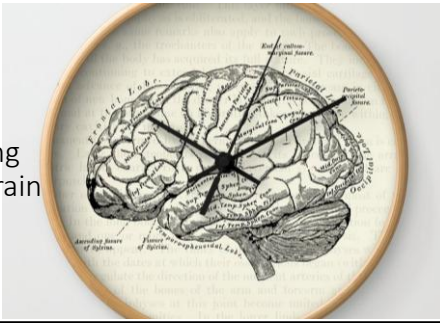
MPs: Adam Brickman & Jennifer Manly

- 2,300 Baseline assessments
- Offspring are from 1,416 families in WHICAP
- Completed follow-up of 47% of the cohort (n = 1,072)
 - 80% of those seen in 2017 & 2018
- Acquired 1,043 MRI scans
 - 854 unique individuals (41% of the cohort)
 - 89 repeat scans for longitudinal analysis
- Biomarkers (missing for ~750 seen during 2020 - 2021)



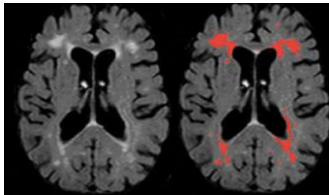
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Weathering and the Brain



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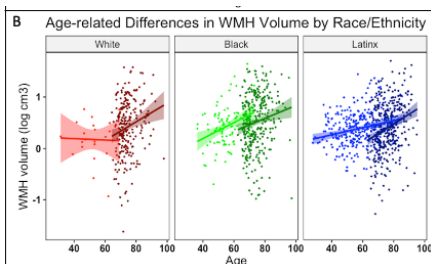
Cerebrovascular disease



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Weathering: White Matter Hyperintensities

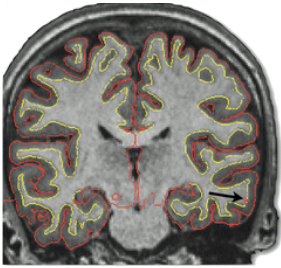
Turney et al., 2023



Indra Turney

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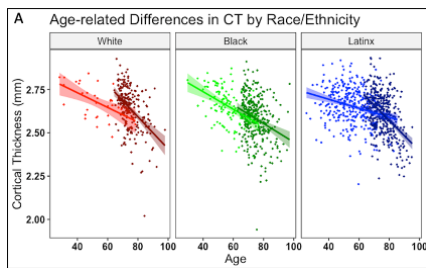
Cortical Thickness



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Weathering: Cortical Thickness

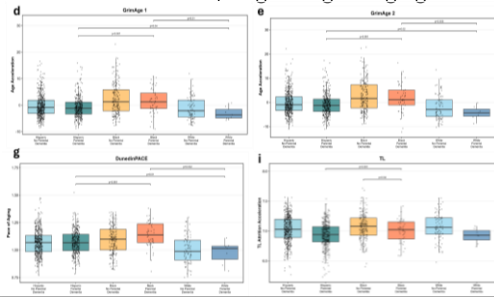
Turney et al., 2023



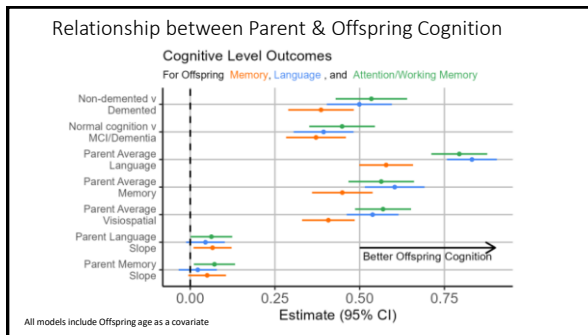
Indra Turney

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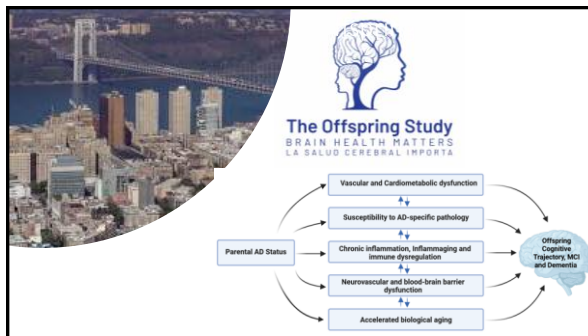
Parental AD and Offspring Biological Aging



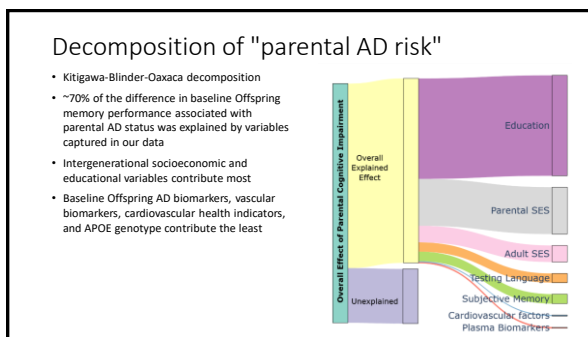
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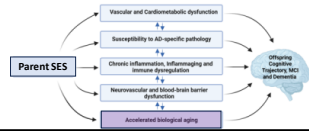
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Rationale for the current analysis

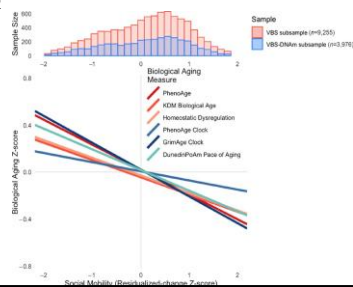
- SES is dominant contributor that explains parent AD-offspring cognition link
 - Lower lifecourse SES linked to poorer cognition and higher dementia risk across many populations
- Biological embedding of early social adversity might explain intergenerational relationship
- DNA methylation can measure accelerated aging



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SES & social mobility are related to biological aging

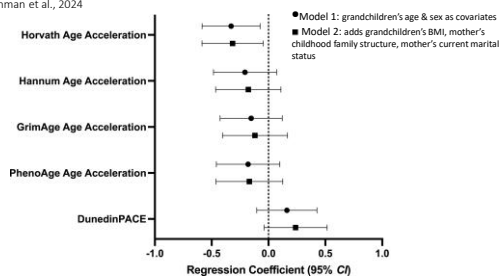
Graf et al., 2022



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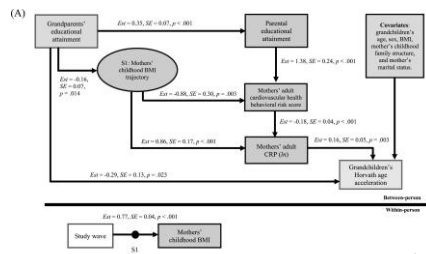
Grandparents' education and epigenetic-based age acceleration in children age 2 - 17

Surachman et al., 2024



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Mediating role of parental education and life course health-related factors

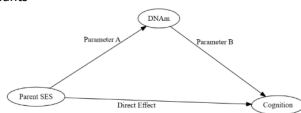


Surachman et al., 2024

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Research questions and hypotheses

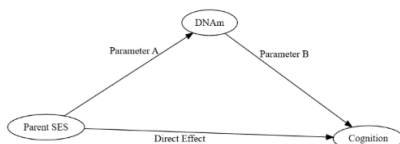
- Replication: is parent social disadvantage reflected biologically in the next generation?
 - H1: Low parent SES will predict offspring epigenetic age acceleration
 - H2: Similar relationship across race and ethnicity
- Does biological aging mediate the relationship between Parent SES and Offspring cognition?
 - H4: Expect partial mediation with DNAm clocks
 - H5: Biological aging will be a stronger mediator in Black and Latinx participants



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Intergenerational Research hypothesis

- Does biological aging mediate the relationship between Parent SES and Offspring cognition?
 - H1: Expect partial mediation with DNAm clocks
 - H2: Biological aging will be a stronger mediator in Black and Latinx participants



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Methods

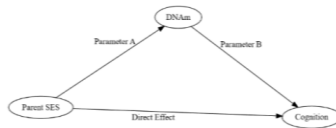
- Who: Offspring cohort with DNA methylation measures (N=1,209)
- Exposure: WHICAP parent SES composite: education, income, occupation
- Offspring DNAm Mediators:
 - GrimAge2: prediction of mortality risk in Framingham
 - DunedinPACE: within-individual decline across 19 biological indicators of organ-system integrity as the predicted phenotype
 - IncDemMRS (Zhang et al., 2025): prediction of incident dementia in Framingham
- Outcome: Offspring baseline cognition
- Covariates:
 - Offspring age
 - Sex/gender



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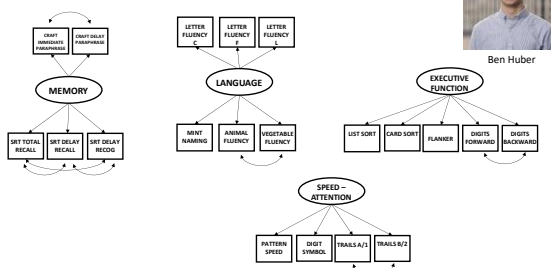
Statistical Analyses

- Mediation models used SEM implemented in lavaan
- Decomposed associations into:
 - a-path: PSES → DNAm
 - b-path: DNAm → cognition
 - c-path: Direct association between PSES and cognition
 - Indirect effect: $a \times b$
- Multiple group SEM to estimate group-specific mediation effects



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Cognitive Outcomes - CFA



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Participant Characteristics

	Overall N = 1,204 ¹	Hispanic or Latino N = 865	Non-Hispanic Black or biracial N = 242	Non-Hispanic White N = 87 ¹	Other Race N = 10 ¹
Baseline Age	56 (11); 28-89	56 (11); 28-89	56 (11); 28-89	54 (12); 28-83	50 (14); 35-73
Female	805 (67%)	597 (69%)	149 (62%)	54 (62%)	5 (50%)
Education (Years)	12.8 (3.7); 0.0-20.0	12.0 (3.8); 0.0-20.0	14.1 (2.5); 6.0-20.0	16.5 (2.0); 12.0-20.0	15.1 (2.8); 10.0-18.0
Parent Education (Years)	8.3 (5.0); 0.0-20.0	6.3 (4.1); 0.0-20.0	13.0 (2.9); 3.0-20.0	14.7 (3.1); 6.0-20.0	13.8 (7.1); 3.0-20.0
% Parent Occupation Professional/Technical	14%	4.9%	30%	53%	50%
Parent Monthly Income	1,079 (898); 450-4,001	771 (491); 450-4,001	1,646 (1,033); 450-4,001	2,553 (1,257); 450-4,001	2,390 (1,611); 450-4,001
Parent SES Factor Score	-0.36 (2.53); -4.85-5.96	-1.42 (1.81); -4.85-5.96	2.07 (1.87); -2.50-5.82	3.26 (1.88); -1.77-5.96	2.29 (3.78); -3.51-5.96
Parent Dementia Score	425 (35%)	371 (43%)	46 (19%)	7 (8.1%)	1 (10%)
Grim2 Age Acceleration	0.0 (5.2); -12.3-22.8	-0.4 (4.7); -11.1-22.2	2.5 (8.3); -12.3-22.8	-2.2 (4.9); -10.3-13.5	-2.6 (4.0); -10.5-4.5
Dunedin PACE Age Acceleration	1.07 (0.12); 0.75-1.52	1.07 (0.11); 0.77-1.52	1.10 (0.12); 0.80-1.38	1.00 (0.13); 0.75-1.30	0.98 (0.12); 0.83-1.17
Incident Dementia DNAm Risk	0.00 (1.00); -3.06-4.70	-0.01 (1.01); -2.98-4.70	0.01 (0.97); -3.06-4.37	0.08 (1.01); -2.43-4.05	-0.35 (0.63); -1.01-0.76

¹Mean (SD); Min-Max; n (%)

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Dunedin PACE Age Acceleration	1.07 (0.12); 0.75-1.52	1.07 (0.11); 0.77-1.52	1.10 (0.12); 0.80-1.38	1.00 (0.13); 0.75-1.30	0.98 (0.12); 0.83-1.17
Incident Dementia DNAm Risk	0.00 (1.00); -3.06-4.70	-0.01 (1.01); -2.98-4.70	0.01 (0.97); -3.06-4.37	0.08 (1.01); -2.43-4.05	-0.35 (0.63); -1.01-0.76

¹Mean (SD); Min-Max; n (%)

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Relationship between Parental SES and
biological aging measures

DNAm Measure	Overall	Hispanic or Latino	Non-Hispanic
GrimAge2	0.035** (0.011 - 0.058)	0.018 (-0.018 - 0.055)	-0.092* (-0.16 - -0.021)
DunedinPACE	-0.02 (-0.043 - 0.003)	-0.027 (-0.064 - 0.011)	-0.13*** (-0.19 - -0.064)

The expected relationship between low parent
SES and accelerated biological aging is present
only in non-Latinx Offspring

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Challenge – bias in training of epigenetic clocks

JOURNAL ARTICLE

Epigenetic clocks and research implications of the lack of data on whom they have been developed: a review of reported and missing sociodemographic characteristics

Sarah Holmes Watkins , Christian Testa, Jarvis T Chen, Immaculata De Vivo, Andrew J Simkin, Kate Tilling, Ana V Diaz Roux, George Davey Smith, Pamela D Waterman, Matthew Suderman ... Show more

Environmental Epigenetics, Volume 9, Issue 1, 2023, dvad005,
<https://doi.org/10.1093/esp/dvad005>

Published: 15 July 2023 Article history

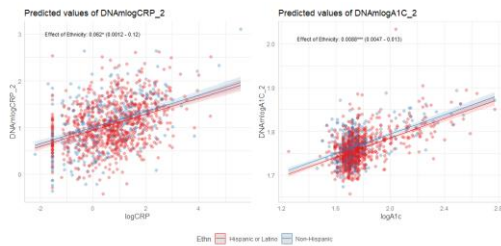
- Prediction models can only learn from the data they see
- Relationship between CpG site and target is may be different in a group underrepresented in the training sample, there is no way for the prediction model to incorporate that



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Metric but not scalar invariance by ethnic group

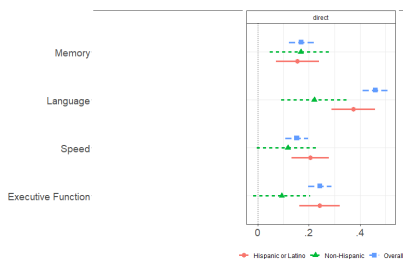
Methylation scores for CRP and HA1c with actual measured biomarkers in Offspring



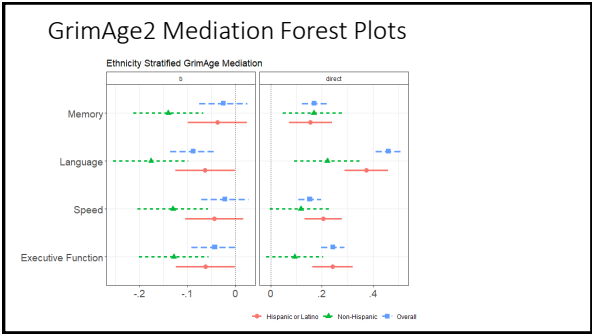
In both cases Latino participants are estimated to have LOWER biomarker levels for the same TRUE biomarker level.

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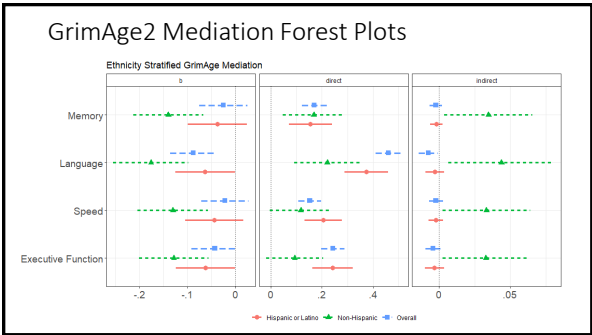
Parent SES → Offspring Cognition Direct Effect



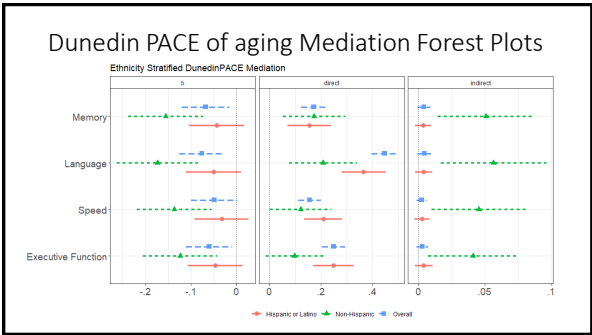
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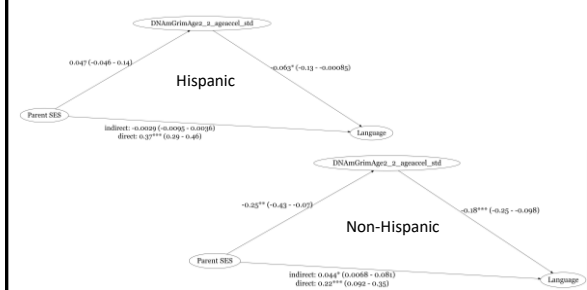
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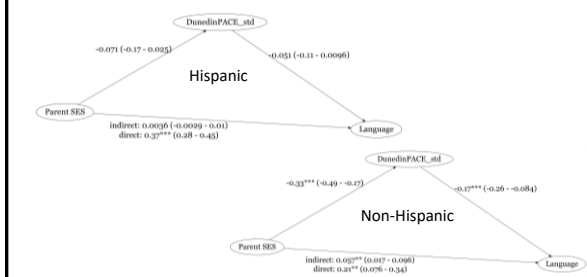


GrimAge Mediation Model Diagrams



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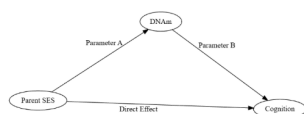
DunedinPACE Mediation Model Diagrams



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Results

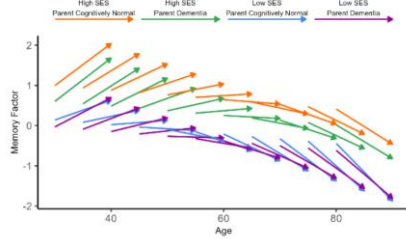
- In some groups, parent social disadvantage reflected biologically in the next generation
 - H1: Low parent SES associated with accelerated offspring epigenetic age BUT
 - H2: Not among Hispanic participants
- Biological aging mediates the relationship between Parent SES and Offspring cognition in non-Latinx participants only
 - H4: Partial mediation with GrimAge2 and DunedinPACE
 - H5: Stronger mediator in non-Hispanic Black and White participants



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Adult SES as a Potential Buffer of the Effect of Parental Dementia Status on Cognitive Trajectory

- SES = education, income, net wealth, occupational status
- Practice effect in young
- Decline with older baseline age
- Effect of parent dementia is weaker among low SES Offspring



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Conclusions & Lessons Learned

- Risk associated with parental dementia is already detectable in midlife
- Parental dementia risk is expressed through multiple biological systems
- Evidence for *heterogeneous* intergenerational social-to-biological embedding
 - *Family history is not destiny*
- Social conditions become biologically embedded across generations
- Accelerated biological aging is one pathway linking intergenerational SES to offspring cognition
 - Vascular mechanisms may be especially important
- Need cross-population biomarker validity
 - Diversity within Latinx Offspring
- Midlife is a critical intervention and prevention window

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