Unraveling Dementia Risk, Brain Health, and Exceptional Cognitive Aging; Clues Across the Life Course

WHI Annual Investigator Meeting
Rebecca Jackson Lecture
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Disclosures

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- Epidemiology Section Editor Alzheimer's and Dementia: Journal of the Alzheimer's Association

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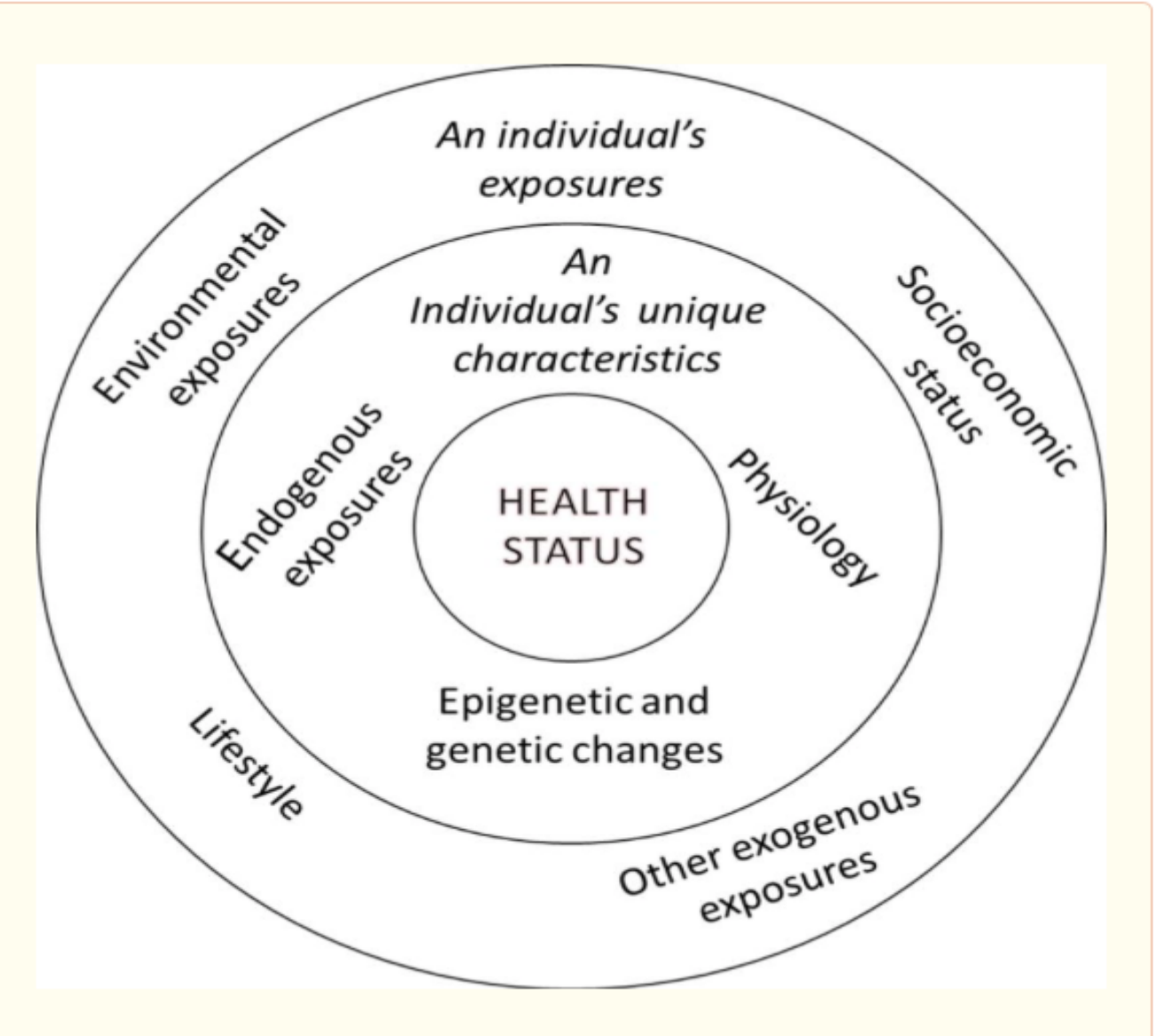
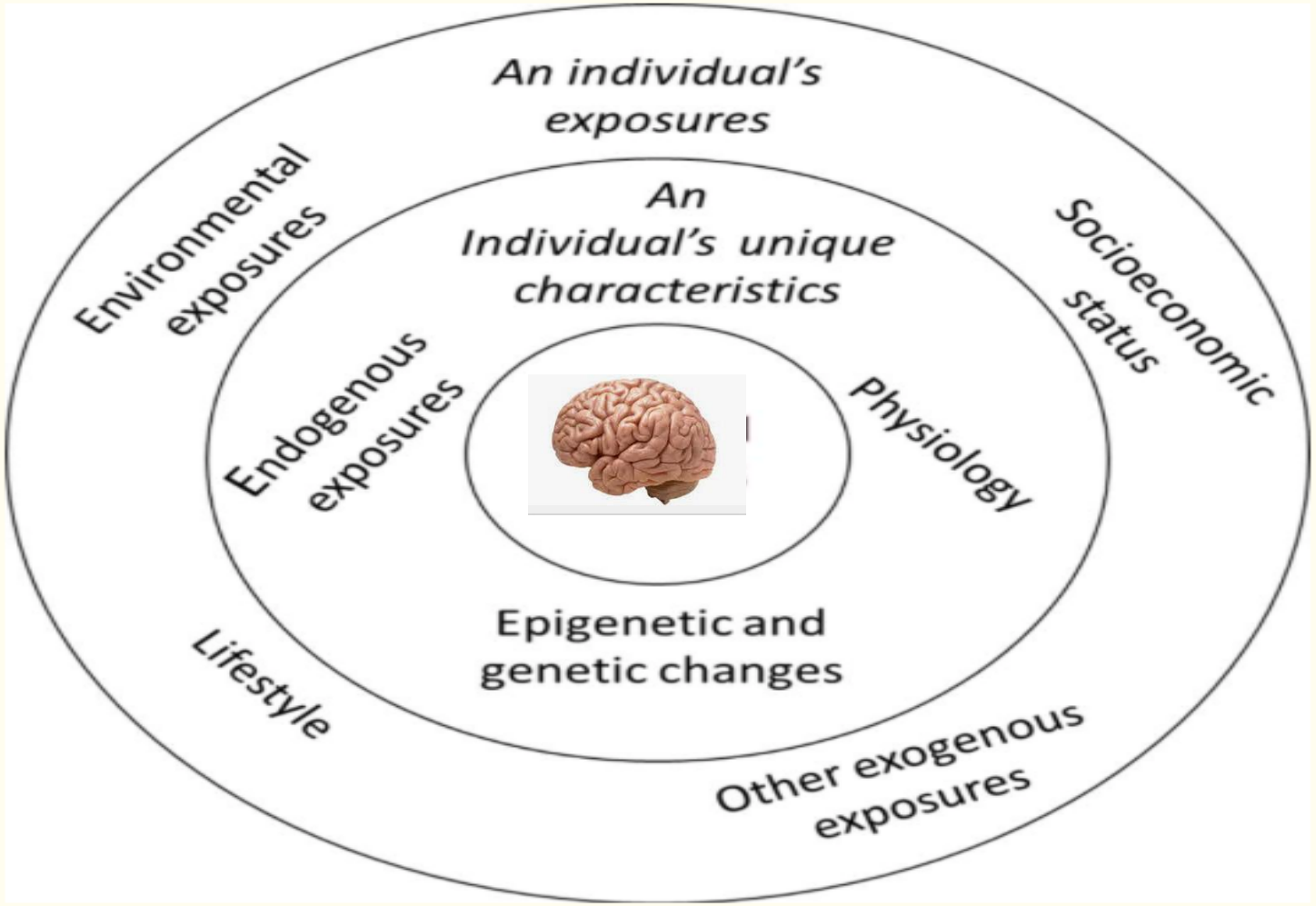
Overview

- Lifecourse and ADRD risk and resilience : When does the clock start ?
- What do we know today about timing of risk factors for AD ?
- How can we conceptualize lifecourse and lifespan exposome in *existing* studies ?
- How can we best apply a lens of equity in lifecourse studies?
- How will this help us understand disparities in ADRD ?
- Exceptional cognitive aging as tool



Use of the "Exposome" in the Practice of Epidemiology: A Primer on -Omic Technologies, *DeBoard G, Am Journal Epidemiology 2016*


An individual's exposures
Environmental exposures
Socioeconomic status
An Individual's unique characteristics
Endogenous exposures
Physiology
Epigenetic and genetic changes
Lifestyle
Other exogenous exposures

- In 2005, Wild defined the exposome as the totality of exposure individuals experience from conception until death and its impact on chronic diseases
- Exposures can include toxicants in the general environment and in workplaces, diet, lifestyle choices and even socioeconomic status
- People have unique characteristics that might make them more or less susceptible to stressors in their environment.
- A person's genetics, epigenetics, health status, and physiology, as well as changes in these personal components caused by previous exposures, can influence the effects of new or present exposures.
- **Disparities in exposures to aspects of the exposome (ie, stress), treatment and screening can augment susceptibility to risk and resilience**

Dynamic

- Several critical life stages have been identified for which some exposures may have a greater impact with respect to future diseases.

- Lifecourse considerations of risk and resilience for AD and related dementias

Lifespan and Lifecourse Considerations for AD Risk and Resilience

- When is the threshold set ? And does it change ?
- Brain changes accumulate over many decades
- Risk factors not the same direction depending on when in the lifecourse they are evaluated
- Are Inflection points different for different populations?

Lifecourse Epidemiology

- True “Birth Cohort” Study
- Gold Standard

RESEARCH Open Access

Identifying dementia using medical data linkage in a longitudinal cohort study: Lothian Birth Cohort 1936

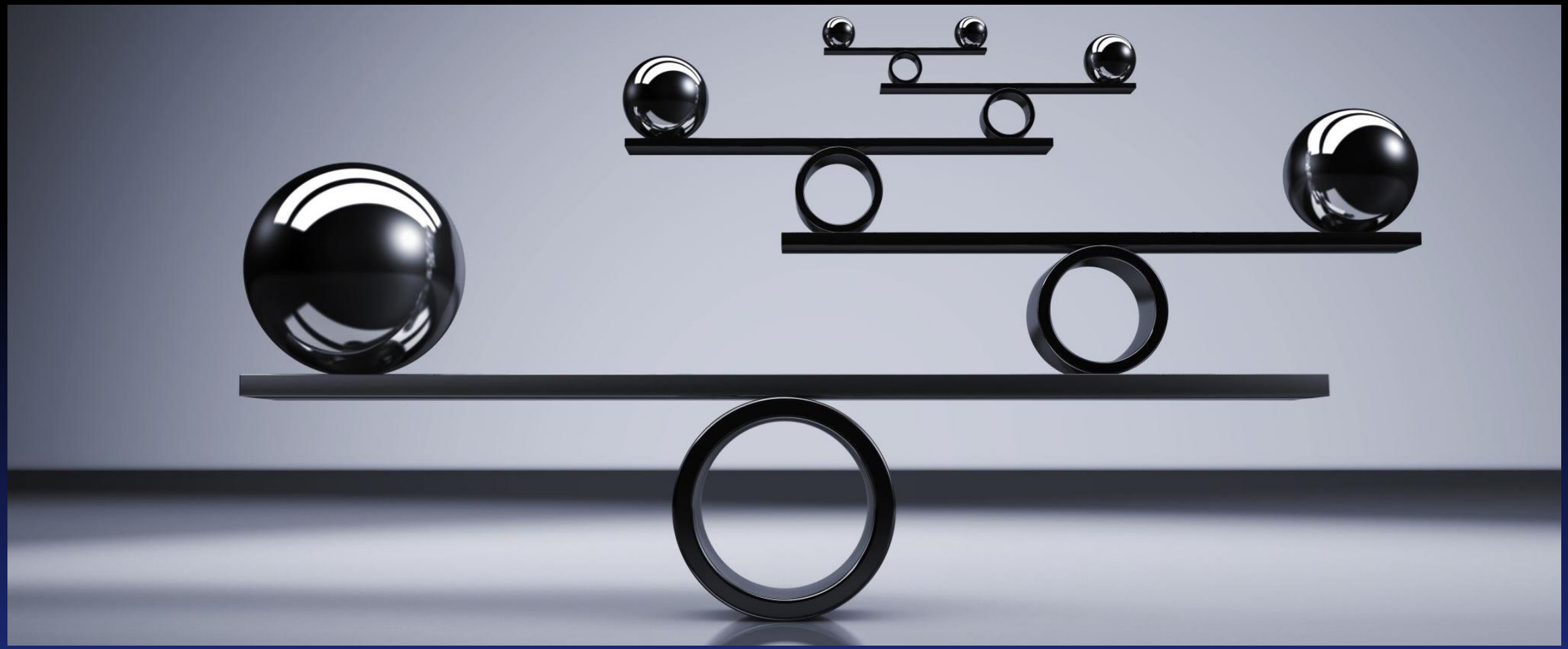
Donncha S. Mullin[1,2,3,4*], Lucy E. Stirland[1,2,5], Emily Buchanan[1,3], Catherine-Anne Convery[1,3], Simon R. Cox[6], Ian J. Deary[6], Cinzia Giuntoli[1,3], Holly Greer[1,3], Danielle Page[6], Elizabeth Robertson[1,3], Susan D. Shenkin[7], Anna Szalek[1,3], Adele Taylor[6], Georgina Weatherdon[1,3], Tim Wilkinson[8,9] and Tom C. Russ[1,2,3,6]

BMJ Open

Identifying the lifetime cognitive and socioeconomic antecedents of cognitive state: seven decades of follow-up in a British birth cohort study

M Richards,[1] Sarah-Naomi James,[1] Alison Sizer,[2] Nikhil Sharma,[1,3] Mark Rawle,[1] Daniel H J Davis,[1] Diana Kuh[1]

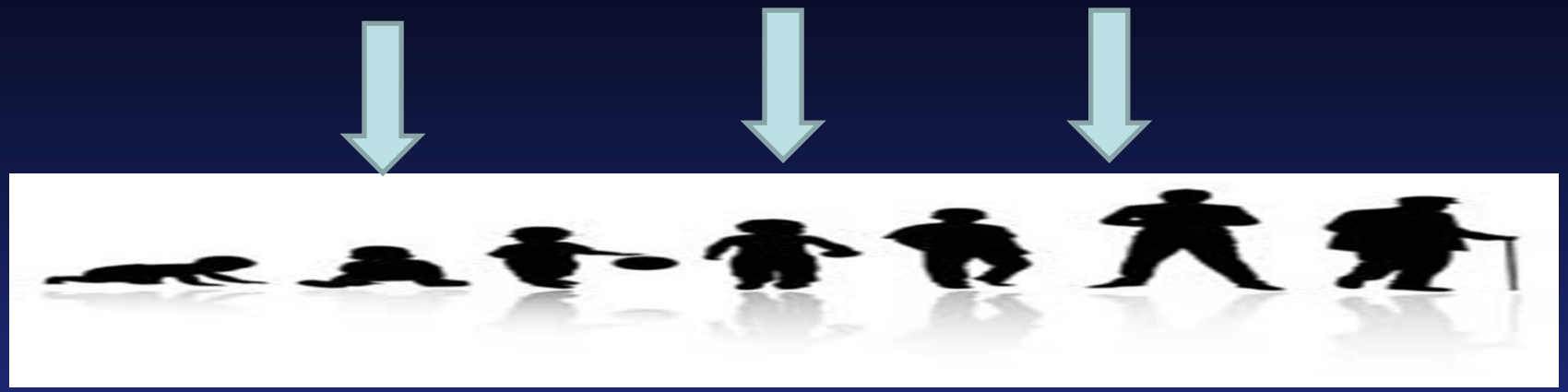
Disadvantages ?



- Cost
- Attrition
- Selection
- Generalizability
- Reflect those at highest risk
- Changing population trends

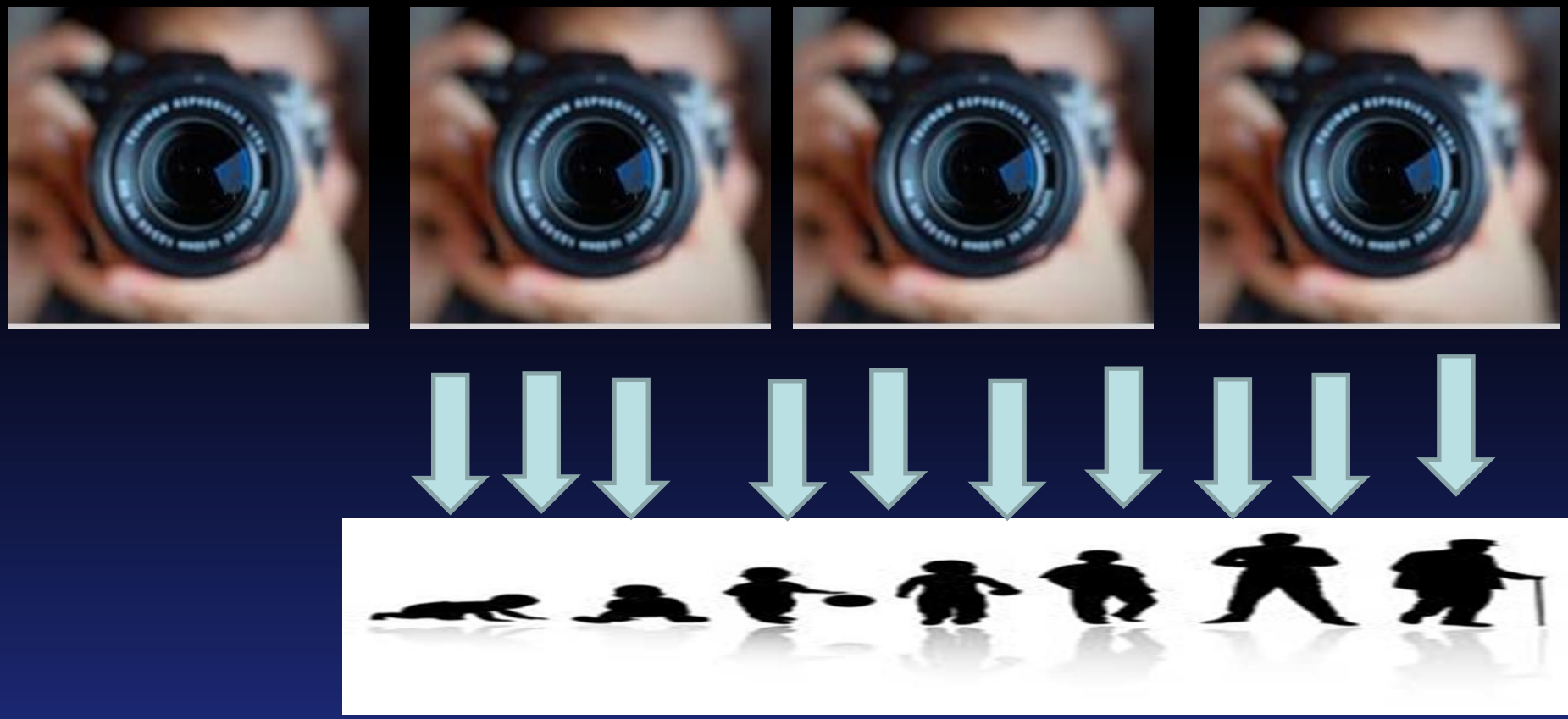
Lifespan AD Risk And Resilience

- Most studies get a snapshot look at exposures that affect ADRD risk *(can we time travel ?)*



Lifespan AD Risk And Resilience

- Leveraging residential address or school attended to link to data sources



Lifespan AD Risk And Resilience: Birth

Opportunities in Cohort Studies

- Air pollution
- Toxic chemicals
- Weather Patterns
- Crime Data
- Green Space
- Food Density
- Area Deprivation index
- Residential segregation

Place of birth has enduring consequences on risk of dementia in a cohort where everyone was living in northern CA by midlife

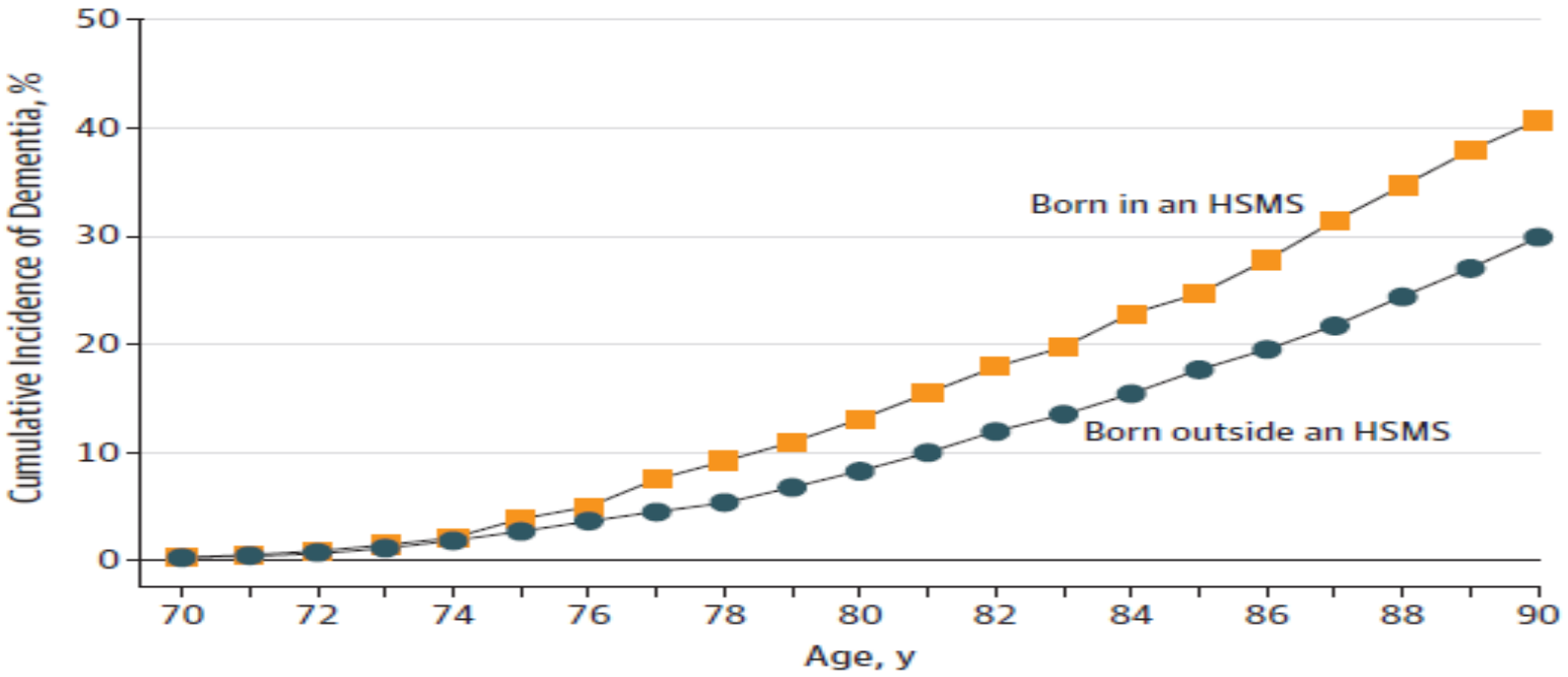
	Born outside a high stroke mortality state		Born in a high stroke mortality state	
	White	Black HR (95% CI)	White HR (95% CI)	Black HR (95% CI)
Age, sex, education and mid-and late- life cardiovascular risk	**Ref**	**1.32 (1.13-1.54)**	**1.43 (1.20-1.70)**	**1.48 (1.31-1.68)**

- Midlife vascular risk factors are body mass index, smoking duration, and hypertension status. Late life cardiovascular risk includes diabetes, hypertension, heart failure, acute myocardial infarction, and stroke.

- ***Gilsanz P, et al, JAMA: Neurology 2017***

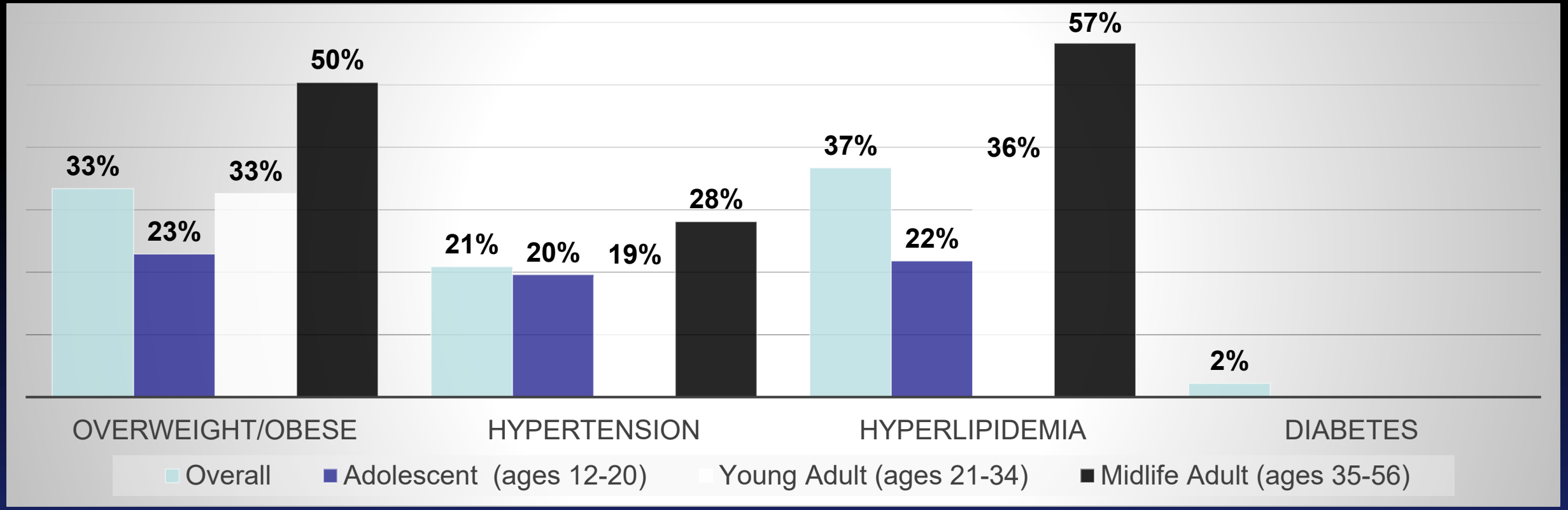
Stroke belt birth and cumulative incidence of dementia

Figure. Cumulative Incidence Dementia Adjusted for Death Rates by Birth Place



HSMS indicates high stroke mortality state.

Medical Records: Cardiovascular Risk Factors are Present for some Before Midlife and are associated with poorer late life cognition : The STAR study

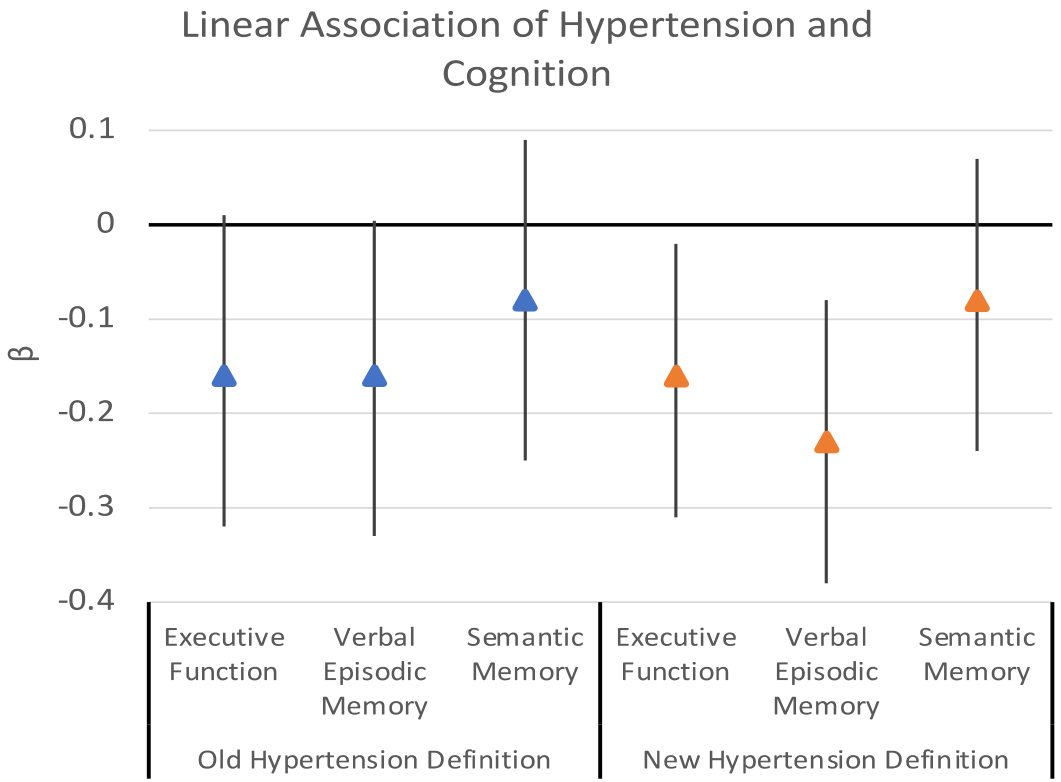


George KM 2022 JAMA Netw Open. 2023

Lifespan AD Risk And Resilience: Young Adulthood

STAR Cohort

	Overall	Adolescents	Young Adults	Midlife Adults
	Ages 12 - 56	Ages 12 - 20	Ages 21 - 34	Ages 35 - 56
	n = 764	n = 169	n = 473	n = 122
Mean Age, years ± SD	26.8 ± 7.3	18.2 ± 1.6	26.7 ± 3.8	39.2 ± 4.1
Male, % (n)	31.7 (242)	24.9 (42)	32.6 (154)	37.7 (46)
Old Hypertension Definition (SPB ≥ 140, DBP ≥ 90, or antihypertensive meds)				
Hypertensive, % (n)	16.5 (126)	18.3 (31)	14.4 (68)	22.1 (27)
New Hypertension Definition (SPB ≥ 130, DBP ≥ 80, or antihypertensive meds)				
Hypertensive, % (n)	21.0 (160)	20.5 (34)	19.2 (91)	28.7 (35)



Association of Racial Residential Segregation Throughout Young Adulthood and Cognitive Performance in Middle-aged Participants in the CARDIA Study

Michelle R. Caunca, PhD[1,2,3,4]; Michelle C. Odden, PhD[5]; M. Maria Glymour, ScD[6]; Tali Elfassy, PhD[1,2]; Kiarri N. Kershaw, PhD[7]; Stephen Sidney, MD, MPH[8]; Kristine Yaffe, MD[6,9,10]; Lenore Launer, PhD[11]; Adina Zeki Al Hazzouri, PhD[12]

Relation between 20-year income volatility and brain health in midlife

The CARDIA study

Leslie Grasset, PhD, M. Maria Glymour, ScD, Tali Elfassy, PhD, Samuel L. Swift, MPH, Kristine Yaffe, MD, Archana Singh-Manoux, PhD, and Adina Zeki Al Hazzouri, PhD

Neurology® 2019;93:e1890-e1899. doi:10.1212/WNL.0000000000008463

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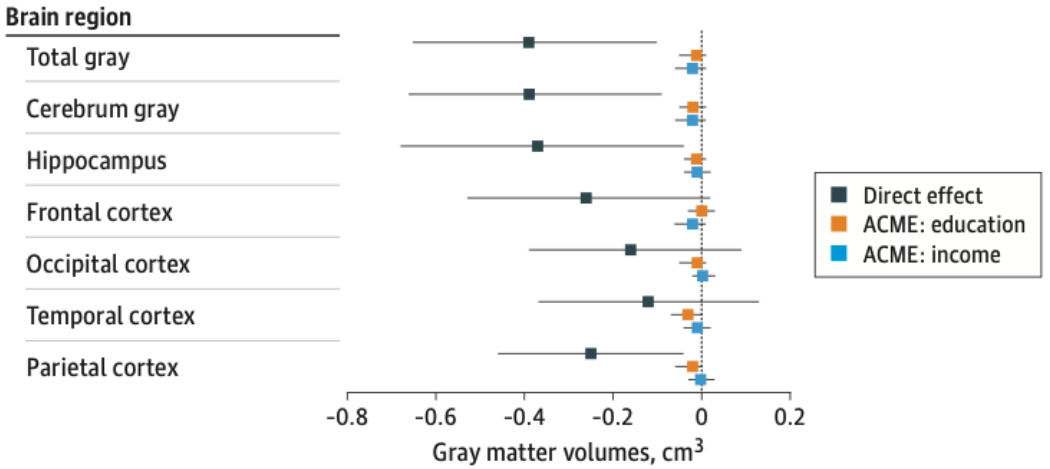
Original Investigation | Public Health

Childhood Community Disadvantage and MRI-Derived Structural Brain Integrity After Age 65 Years

Rachel L. Peterson, PhD, MPH, MA; Erika Meza, PhD; Kristen M. George, PhD; Pauline Maillard, PhD; Charles DeCarli, MD; Paola Gilsanz, ScD; Yenee Soh, ScD; Yi Lor, MPH; Amy J. Kind, MD, PhD; Lisa L. Barnes, PhD; Rachel A. Whitmer, PhD

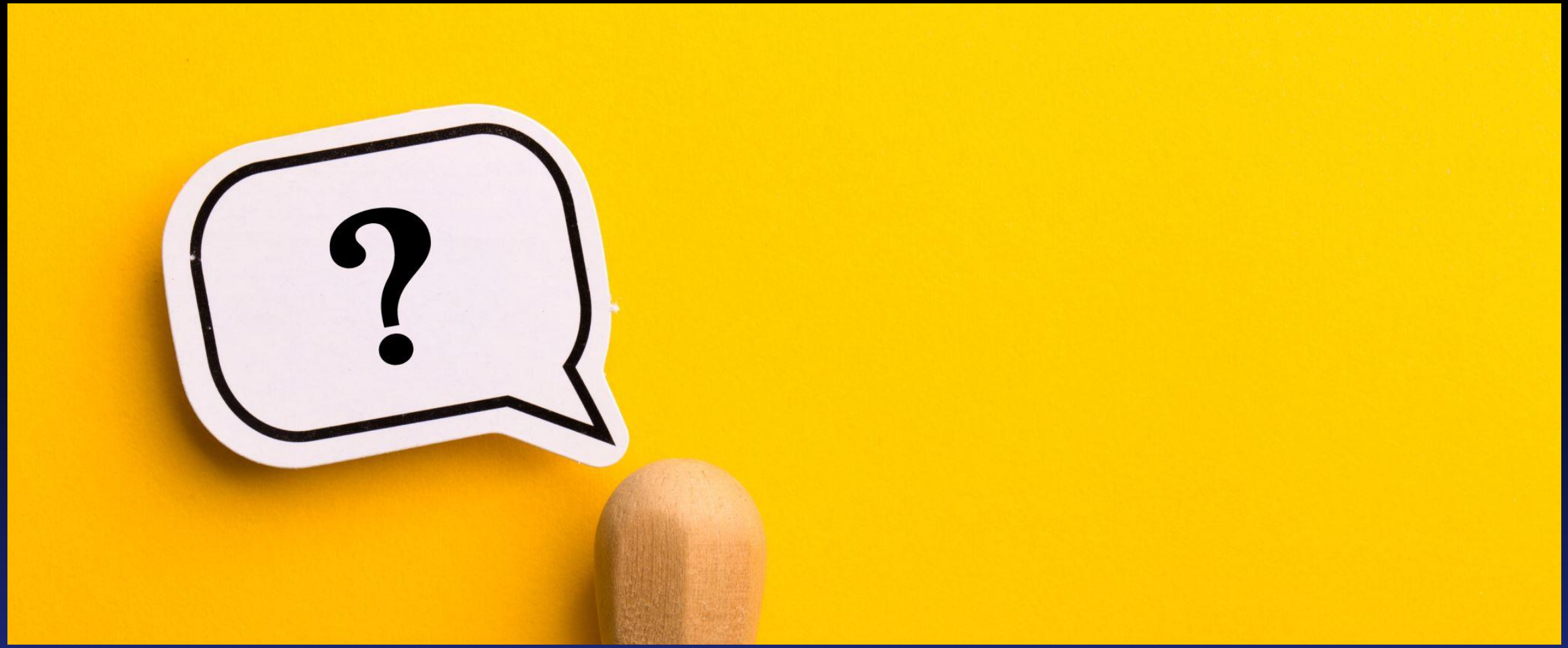
Figure 1. Estimated Average Direct Effects of Childhood Community Disadvantage on Late-Life Gray Matter Volumes and Average Causal Mediated Effects (ACME) of Education and Income on the Association of Childhood Community Disadvantage and Late-Life Gray Matter Volumes



All models adjusted for sex, race and ethnicity, and parental educational attainment.

Childhood community disadvantage was associated with worse late-life brain health independent of individual socioeconomic status.

Asking the Right Questions



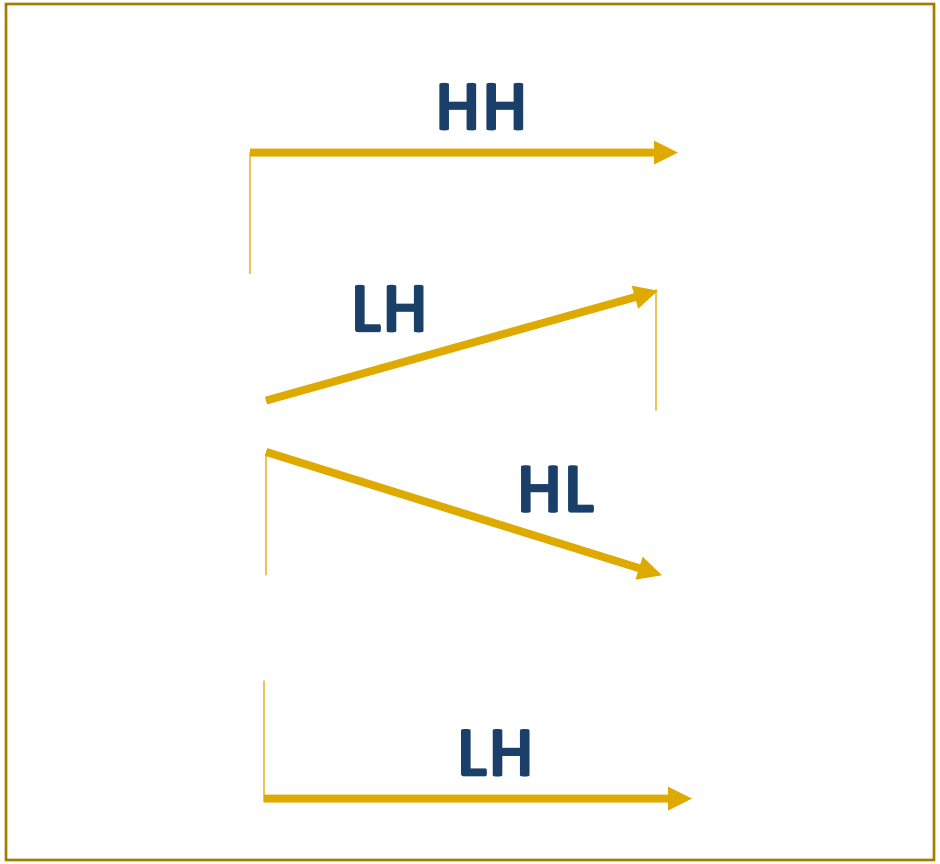
Lifecourse SES Trajectories

	Childhood	Late Adulthood
Financial Capital	Ever went hungry because there wasn't enough money to buy food.	Always or often worry: not enough money for expenses AND income <US$75k
	Parents did not own childhood home AND Prior to age 16 family was poor vs. well off or average.	Receives federal SSI or state welfare, help from friends/family and/or earns <US$55K
Cultural Capital	One or both parents has ≤8th grade education	Participant has ≤High School education
Social Capital	Never/rarely had someone in whom could trust and confide.	Currently has someone in whom they can trust and depend.

Theorized using Bourdieu's "Forms of Capital"

Lifecourse SES Trajectories

- consistently high (HH)
- low childhood/high adult (LH)
- high childhood/low adult (HL)
- consistently low (LL)



Lifecourse SES Trajectories and Late-Life Cognition

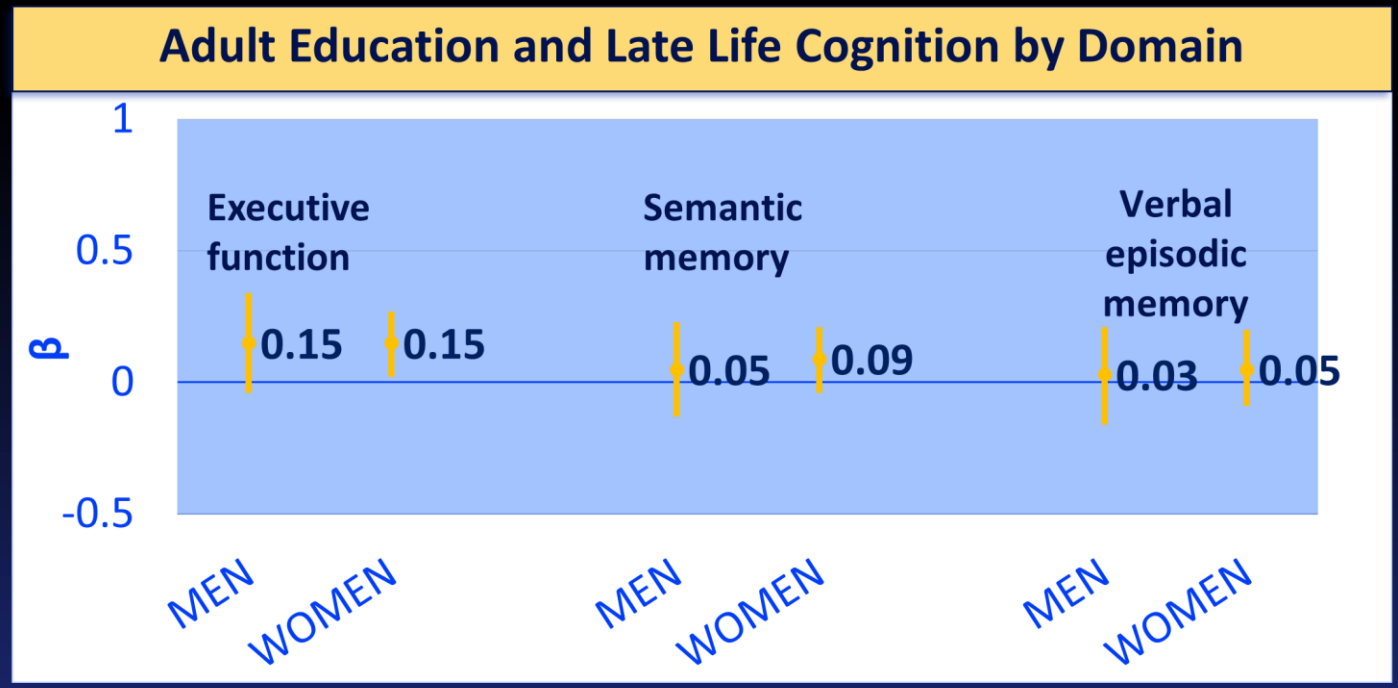
	Global Cognition β (95% CI)
Financial Capital	
Low Lifecourse SES	ref.
Low Childhood, High Adult SES	0.18 (0.02, 0.33)
High Childhood, Low Adult SES	0.04 (-0.11, 0.18)
High Lifecourse SES	0.30 (0.17, 0.43)
Cultural Capital	
Low Lifecourse SES	ref.
Low Childhood, High Adult SES	0.55 (0.40, 0.70)
High Childhood, Low Adult SES	0.11 (-0.14, 0.35)
High Lifecourse SES	0.76 (0.61, 0.91)
Social Capital	
Low Lifecourse SES	ref.
Low Childhood, High Adult SES	0.27 (0.08, 0.45)
High Childhood, Low Adult SES	0.19 (-0.05, 0.44)
High Lifecourse SES	0.29 (0.12, 0.47)

All models adjusted for age, gender, and race/ethnicity

Peterson RL, .BMC Public Health. 2021 May 13;21(1):920. doi: 10.1186/s12889-021-10976-6.

Later-Life Education and Late-Life Cognition in KHANDLE Study

Women were more likely to obtain education during adulthood than men (37.3% vs 27%). Education during adulthood was associated with higher executive function scores in late life.



KHANDLE STUDY
Kaiser Healthy Aging and Diverse Life Experiences

Soh Y, Alzheimers Dement. 2024 Jan;20

October 31, 2017; 89 (18) ARTICLE

Neurology®

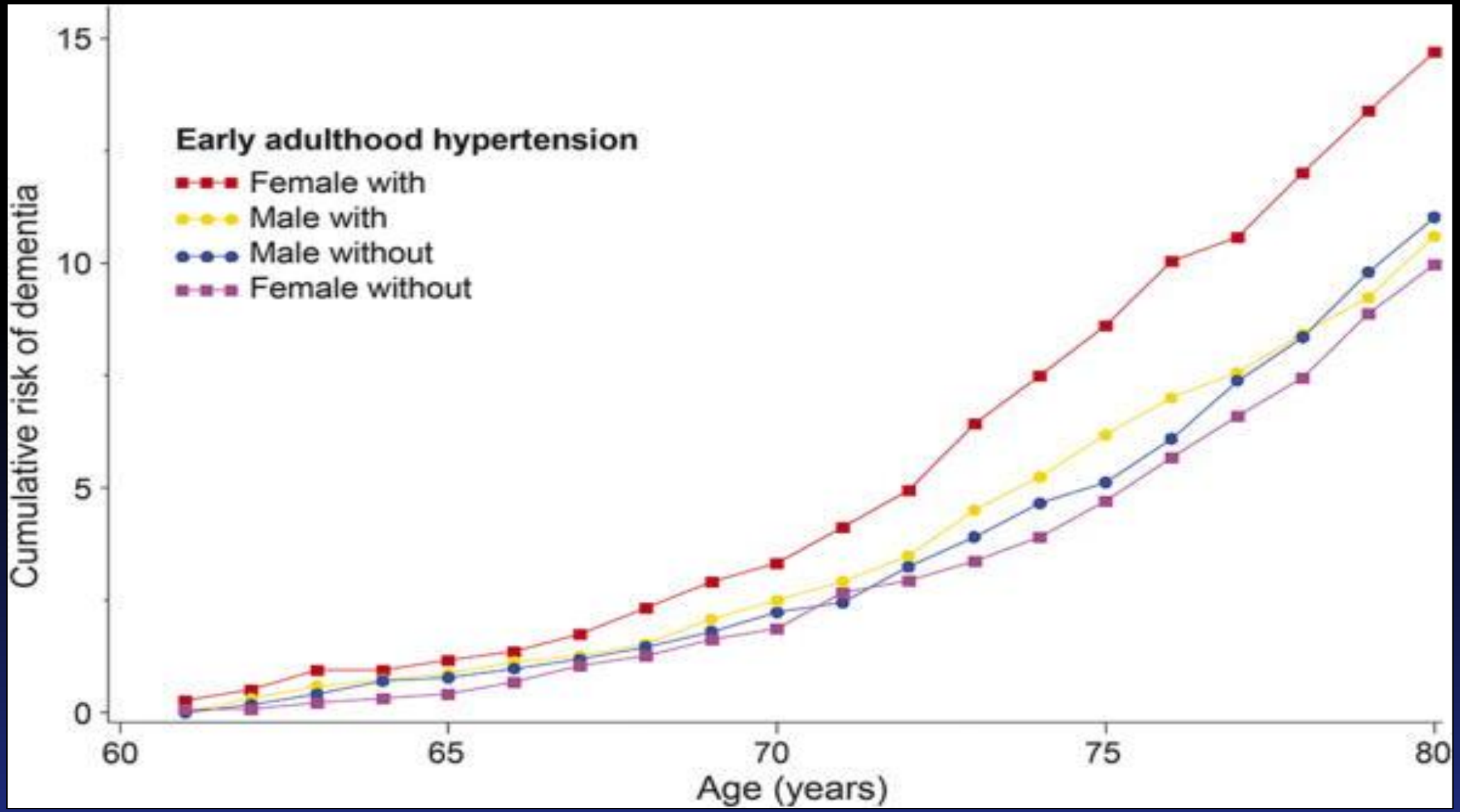
Female sex, early-onset hypertension, and risk of dementia

Paola Gilsanz, Elizabeth Rose Mayeda, M. Maria Glymour, Charles P. Quesenberry, Dan M. Mungas, Charles DeCarli, Alexander Dean, Rachel A. Whitmer

First published October 4, 2017, DOI: https://doi.org/10.1212/WNL.0000000000004602

- Previous studies have found midlife blood pressure is associated with dementia but no studies examining young adulthood.
- How is blood pressure in young adulthood associated with dementia?
- How is hypertension change in young adulthood associated with dementia?

Cumulative incidence of dementia by sex and early adulthood hypertension status (Neurology, 2017)

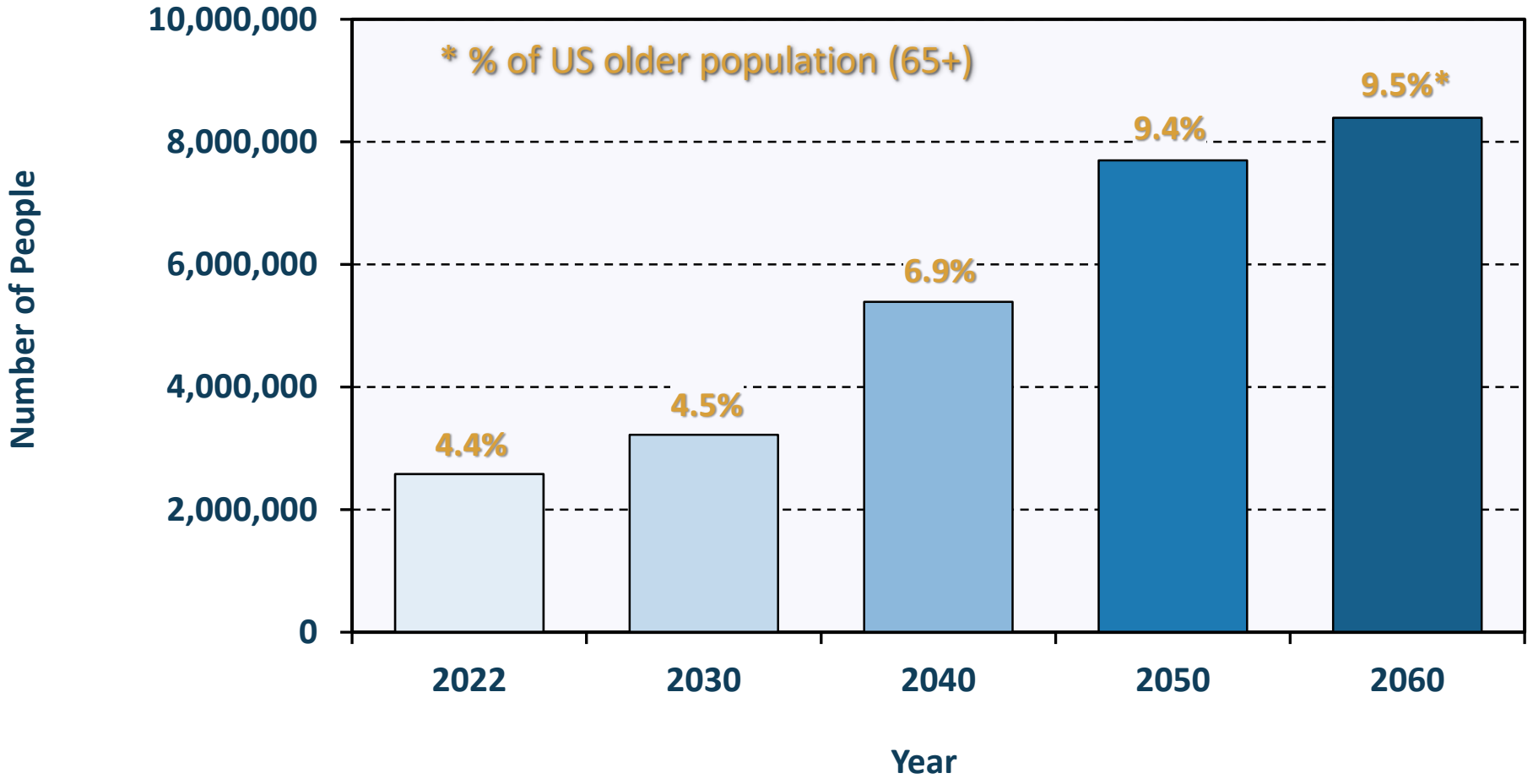


Hypertension in adulthood, sex, and dementia risk

- Though mid adulthood hypertension was more common in men, it was only associated with dementia risk in women.
- Onset of hypertension and persistent hypertension predicted higher dementia risk in women compared to stable normotensive.
- Sex differences in the timing of dementia risk factors have important implications for brain health.

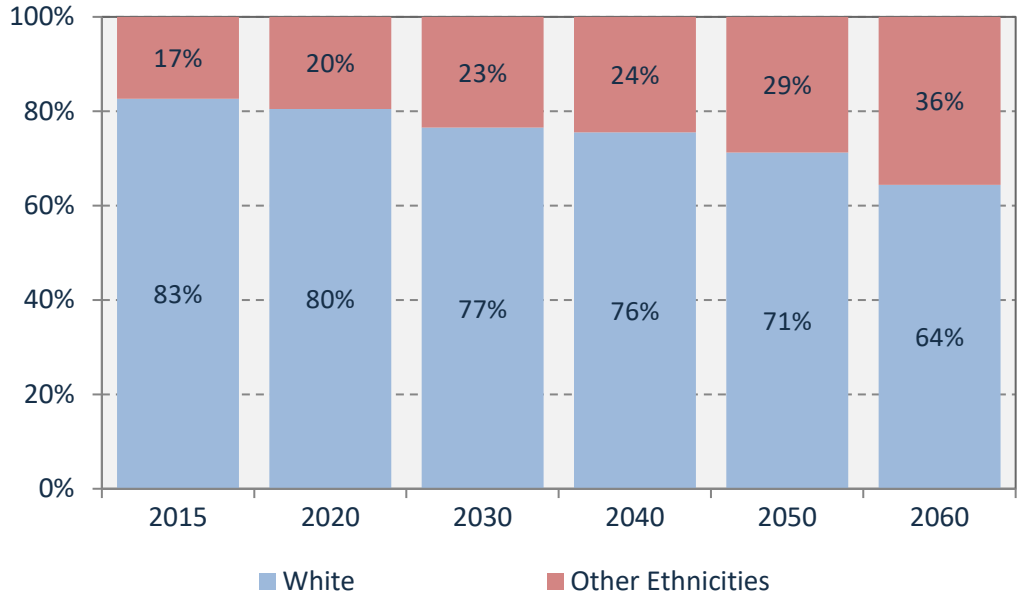
What can in vivo biomarkers tell us about lifecourse timing of risk and resilience to ADRD ?

U.S. Projected Population Growth Among 90+ Year Olds

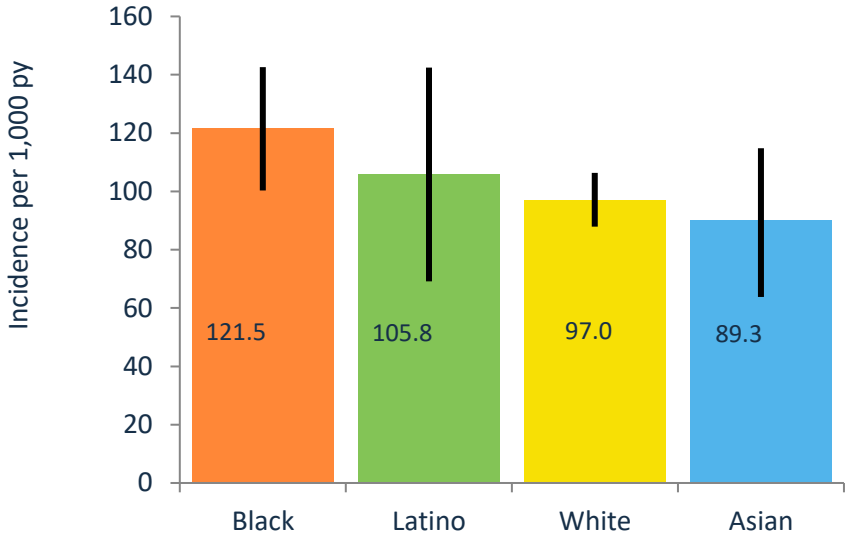


Projected Population by Five-Year Age Group and Sex for the United States, Main Series: 2022-2100. (NP2023-T3)
U.S. Census Bureau. Population Division. November 2023.

Ethnoracial Diversity and Dementia Risk among the 90+ Population



Increasing percentage of ethnicities other than White in the 90+ population in the US[1]



From Kaiser EHR, differences in incidence rates of dementia by racial/ethnic groups[2]

[1]US Census Bureau Projected Population by Single Year of Age, Sex, Race, and Hispanic Origin 2014 to 2060 (Table 1)
[2]P Gilsanz , et al, Alz & Dementia, 2019; 15:497-505

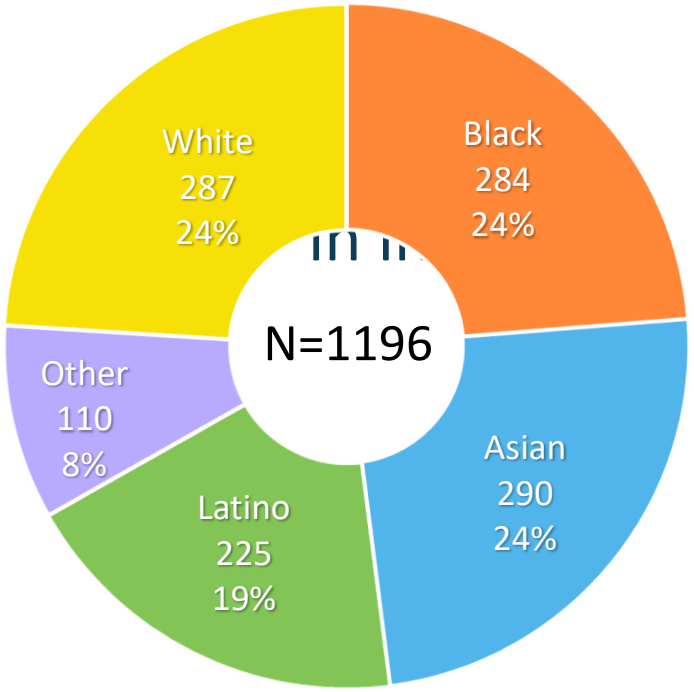
LIFE After 90

LIFE After 90

MPIs: Rachel Whitmer, María Corrada, Paola Gilsanz

- Ongoing multiracial cohort of oldest-old individuals
- Inclusion Criteria
  - Long-time members of the Kaiser Permanente Northern California Health Care System
  - English or Spanish Proficiency
  - No dementia diagnosis, dialysis, or hospice their medical record at the time of recruitment
- Enrollment began July 2018

Optional imaging (n=247) and brain donation (n=134)

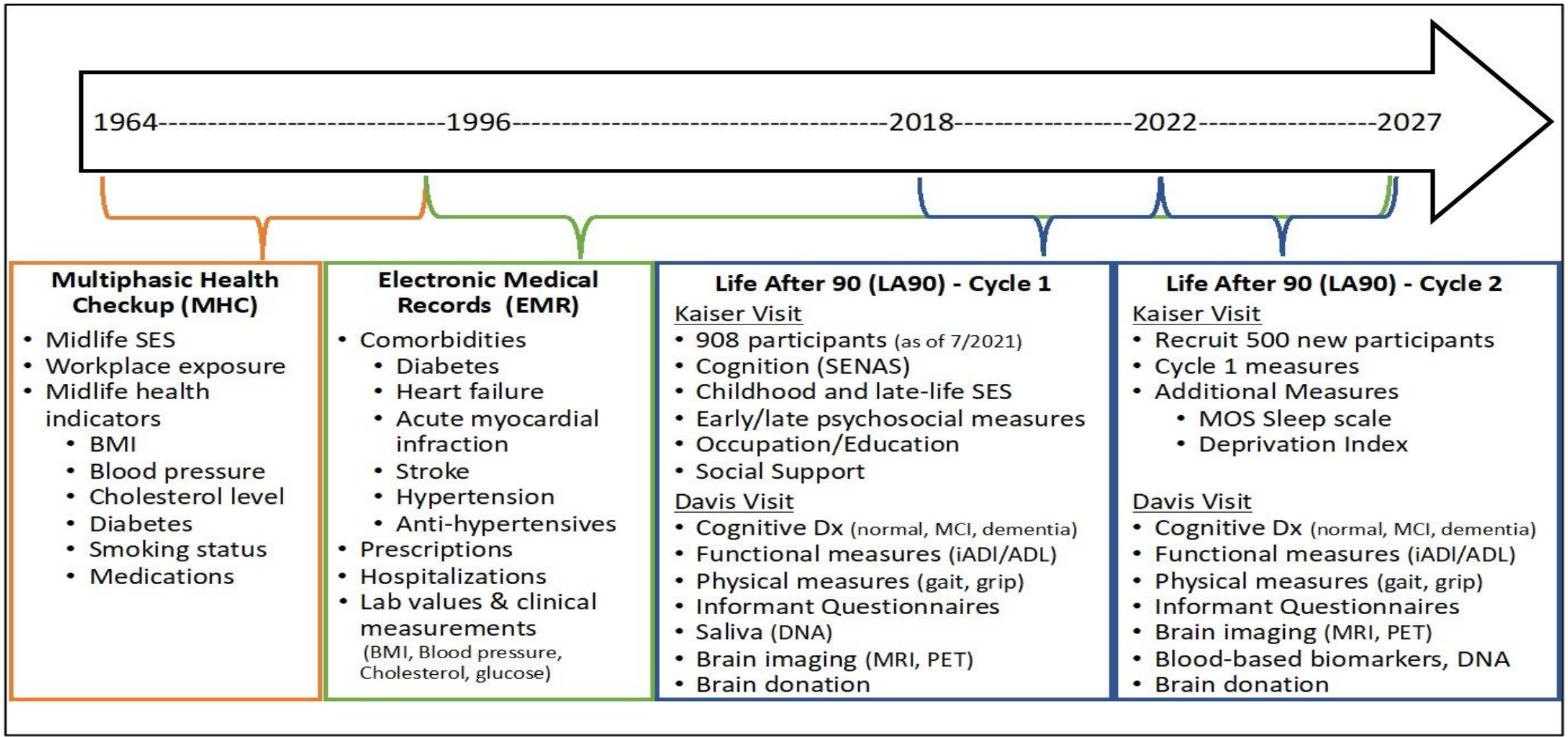


Co-investigators
UC Davis: C DeCarli, D Mungas, B Dugger, LW Jin
Kaiser: C Quesenberry
Boston U: M Glymour
UCI: C Kawas

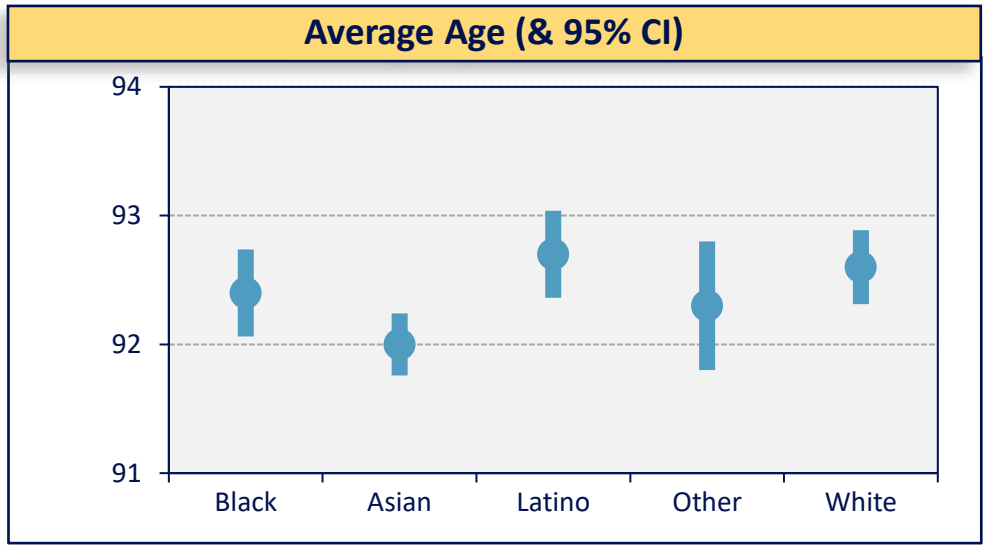
LIFE After 90

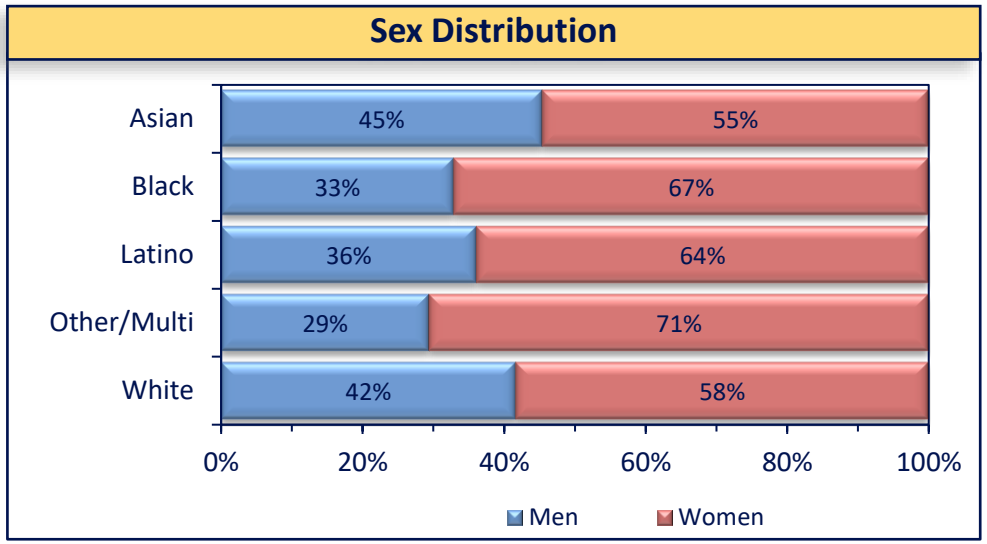
LIFE After 90

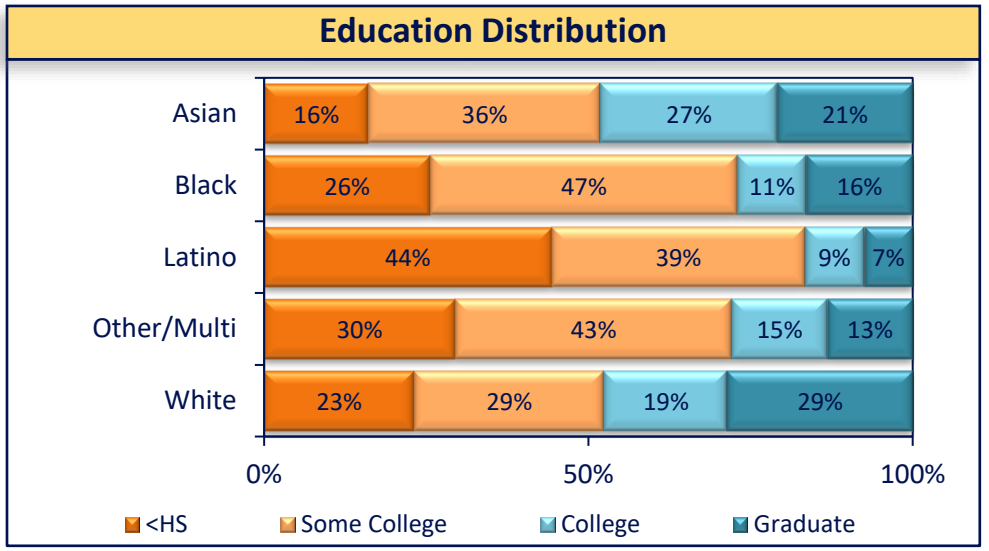
- Evaluations at home
- Evaluations every 6 months
- Shorter assessments

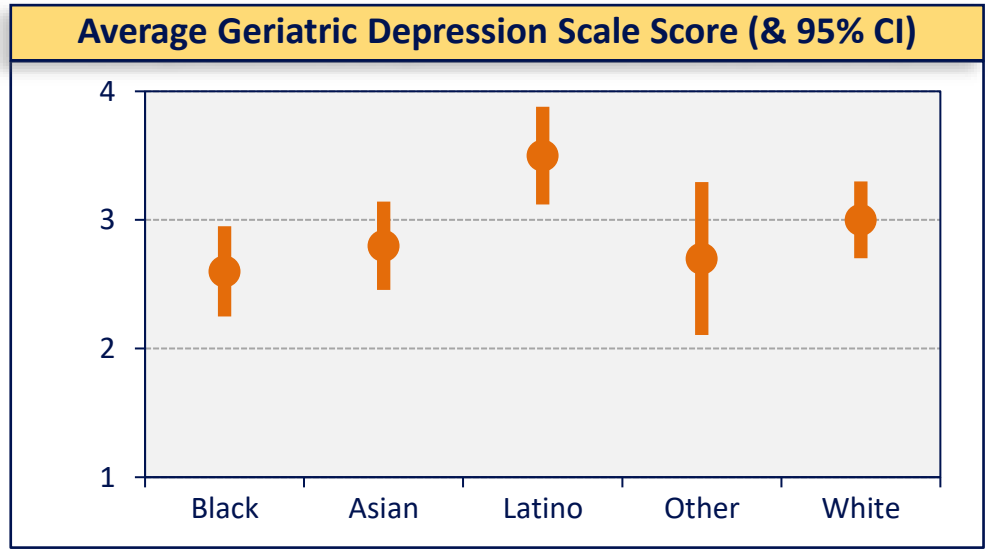


Participant Characteristics at Baseline (N=999)





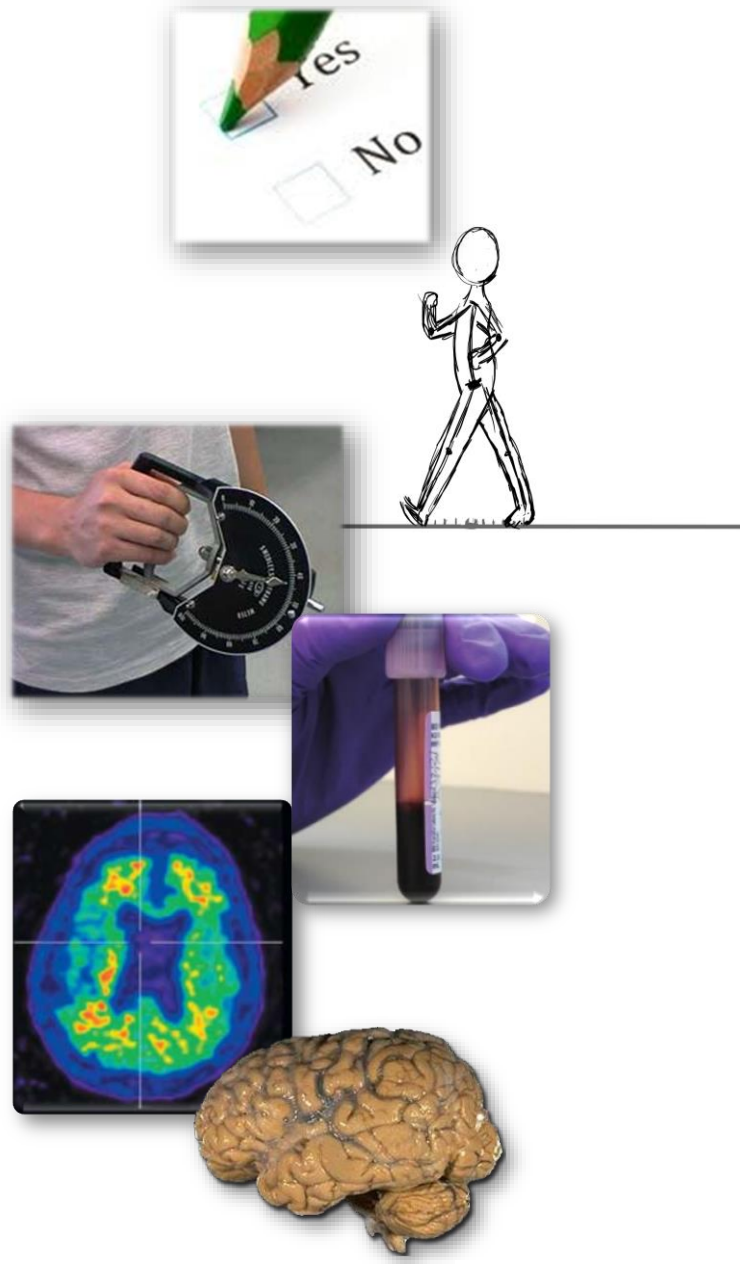




Assessments

Frequent (6 months), short, at home

- Demographics & Medical History
- SENAS neuropsychological battery
- Neurological & Physical Examination
- Informant Questionnaires
- Saliva for DNA studies (n=550)
- Brain Imaging
  - Amyloid PET (N=259), MRI (N=277)
- Brain Donation (n=134)



LIFE After 90

Conclusions

In this diverse cohort with exceptional longevity there were differences in domain specific cognitive reserve by sex and amyloid positivity

Lower education and higher age trended towards less cognitive reserve

Risk and resilience to AD may have specific patterns after age 90

Lifecourse Studies : Selection Bias and Attrition

- Characteristics of participants who opt out of participating in a given study are typically unknown

- True extent of selection bias is difficult to determine (Ganguli et al., 2015).

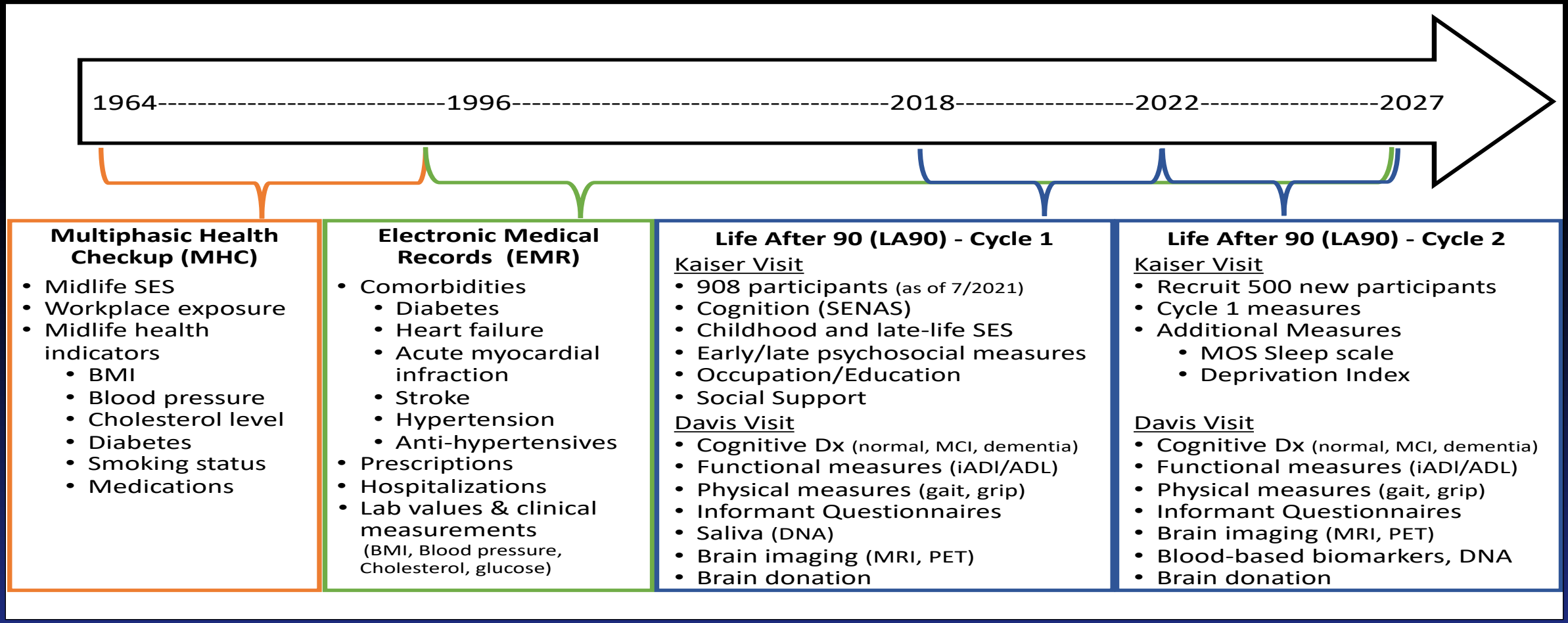
Brain Imaging Behav. 2015 Jun; 9(2): 204–212.
PMID: 24573773
doi: 10.1007/s11682-014-9297-9

WHO WANTS A FREE BRAIN SCAN? ASSESSING AND CORRECTING FOR RECRUITMENT BIASES IN A POPULATION-BASED sMRI PILOT STUDY

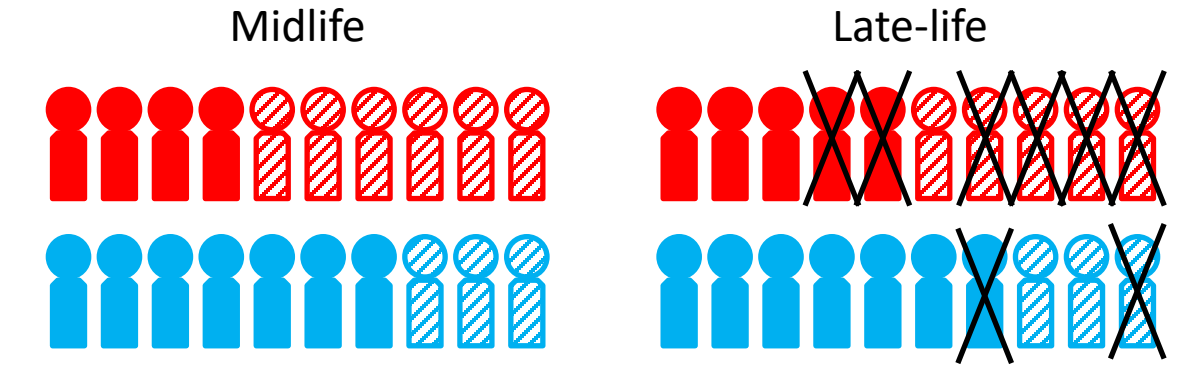
Mary Ganguli,[1,2,3] Ching-Wen Lee,[1] Tiffany Hughes,[1] Beth E. Snitz,[2] Jennifer Jakubcak,[1] Ranjan Duara,[4,5,6,7] and Chung-Chou H. Chang[8,9]

Example : Inverse Probability Weighting for Selection into a Cohort Study Nested in a HealthCare Population: The *LifeAfter90 Study*

Figure 9. Timing of Data Collection and Data Sources



Hypertension and Risk of Dementia: Bias from Differential Survival



This diagram represents that although the causal RR for hypertension on dementia is 2.0, due to selective survival, no association between hypertension and dementia is observed among people who survive to late-life.

slide credit : *Mayeda ER 2017*

Inverse Probability Weights (IPW)

- Informally, weighting by IPWs up-weights individuals who, given their history of covariates exposure, were unlikely to survive, be KPNC members, and enroll in LA90; assuming no unobserved confounding, the weighting adjusts for differential survival, KP membership dropout, and enrolment into LA90.

Goal

Create IPWs for survival, membership, and for participation

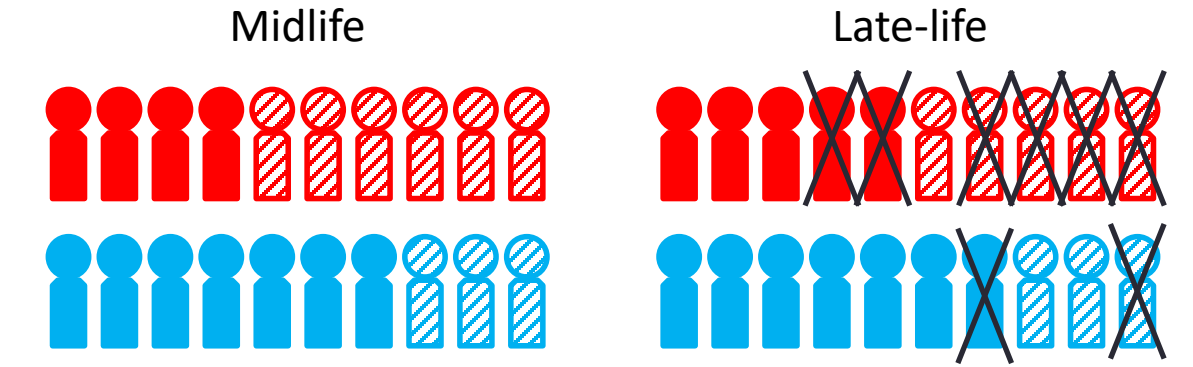
- Weighted by inverse probability of being in the LA90 sample
- Adjusted for age at 1964 , sex, race, and education
- Adjusted for age at 1964 , sex, race, education and hypertension

$$IPSW_i = \frac{1}{Pr[Survival_{2018i} | C_{MHCi}]}$$

$$IPKPW_i = \frac{1}{Pr[Membership_{2017i} | Survival_{2018} = 1, C_{MHCi}]}$$

- $$IPPartW_i = \frac{1}{Pr[Participate\ in\ LA90_{2018i} | Survival_{2017}=1, Membership=1, C_{MHCi}]}$$

Hypertension and Risk of Dementia: Bias from Differential Survival



This diagram represents that although the causal RR for hypertension on dementia is 2.0, due to selective survival, no association between hypertension and dementia is observed among people who survive to late-life.

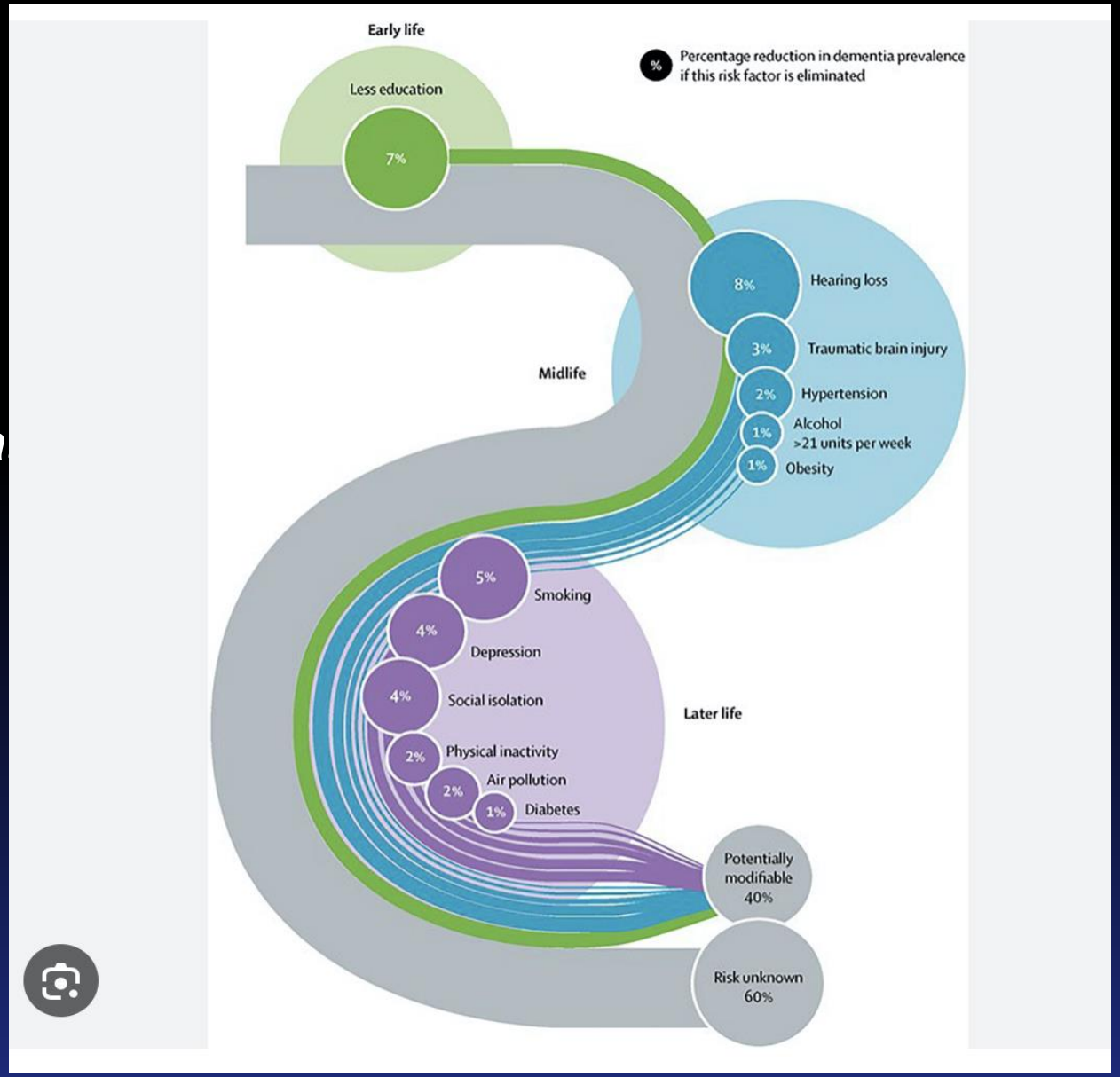
slide credit : *Mayeda ER 2017*

Survival Bias: Age

- Have to be age 65 to be in most studies of ADRD

Why does that matter and how does tha influence what we know TODAY about risk and resilience to ADRD?

- Population trends in life expectancy, mortality, risk factors



Midlife CVD Risk Factors and Dementia: CAIDE Risk Score

Step 1

Age, y	points
40-46	0
47-53	3
54-55	4

Step 2

Education, y	points
0-6	3
7-9	2
>9	0

Step 3

Sex	points
Men	1
Female	0

Step 4

Cholesterol mg/dL	points
<251	0
≥251	2

Step 5

BMI kg/m	points
<30	0
≥ 30	2

Step 6

Systolic blood Pressure, mm/Hg	points
<140	0
>140	2

Predicted 40-year Risk of dementia

Total points	40-year risk, %
0-1	10
2	11
3	15
4	17
5	20
6	21
7	25
8 -14	29

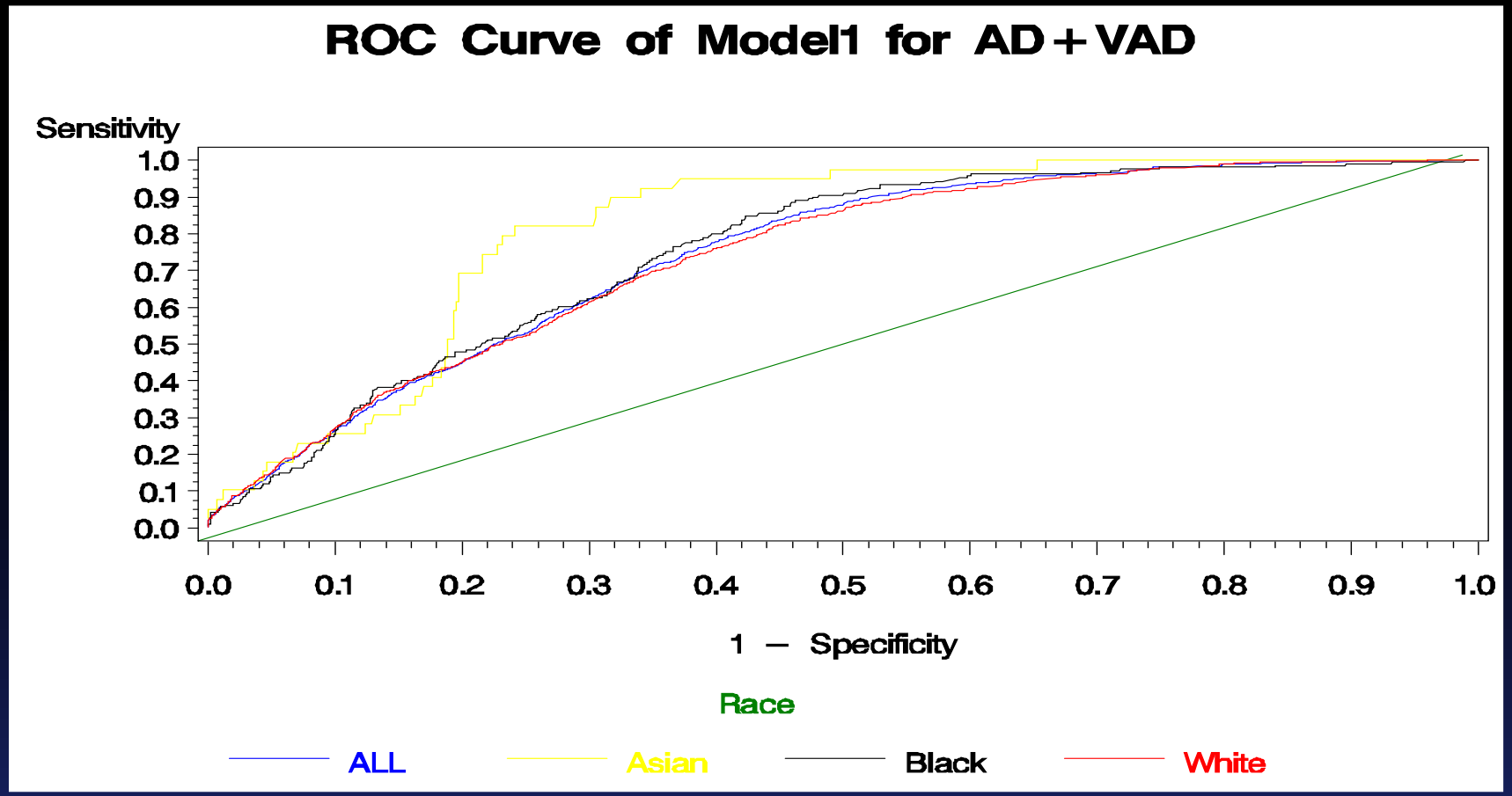
Add up points from stept 1 through 6

Look up predicted 40-year risk of dementia

Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study

Kivipelto M, et al 2006 Lancet Neurology

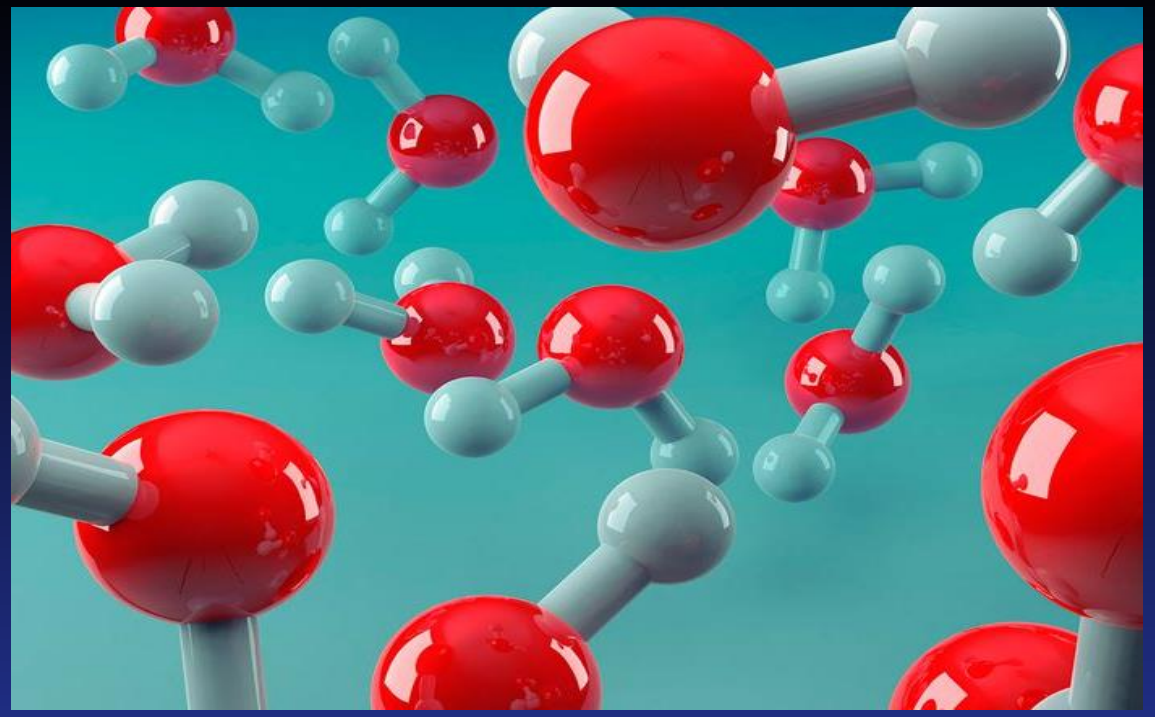
CAIDE Dementia Risk Score Validation:
A score of age, gender, hypertension, hyperlipidemia and high BMI is highly predictive of dementia 30-40 yrs later



Overall AUC .74
Asian: 0.813
Black: 0.751
White: 0.737

Exalto LG Alzheimer's Dementia 2014

Where to next ?



- Leveraging and linking of existing data to quantify the exposures in studies of ADRD risk and resilience in diverse cohorts
- Modeling of inflection points and timing
- Conceptual view of individual differences in susceptibility
- Geocoding , linkages, medical records, asking the right questions
- Harmonizing of data
- Weighting and calibration of the larger population study is based in
- Applying methods for selection bias and attrition to fully appreciate lifcourse on ADRD
- Studies in early adulthood and midlife

THANK YOU !