Charting the Course: Identifying Challenges and Future Directions in Understanding the Links between Early and Midlife Exposures on Late Life Cognitive Health

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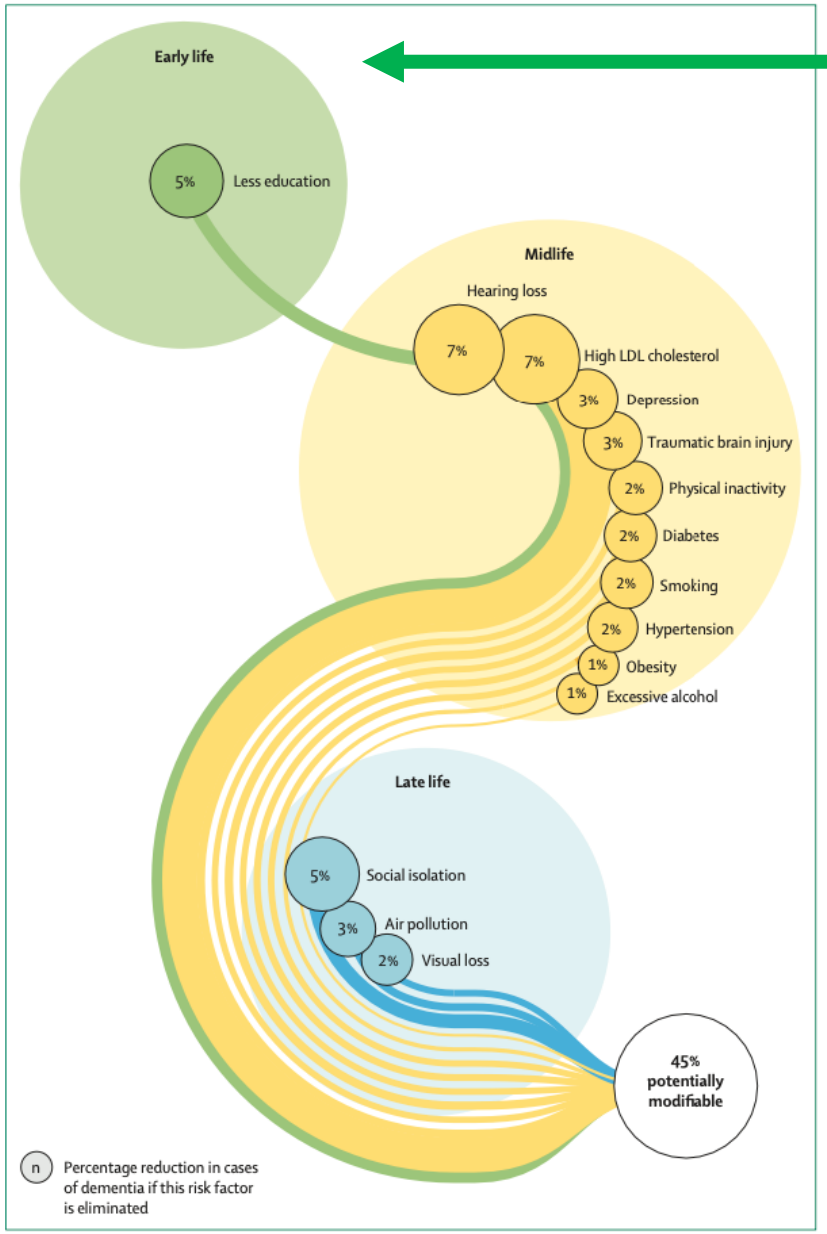
Early life, Midlife, and Late life Modifiable Factors for Dementia



Parental SES

Nutrition

Parental Socioemotional Influence

Genes

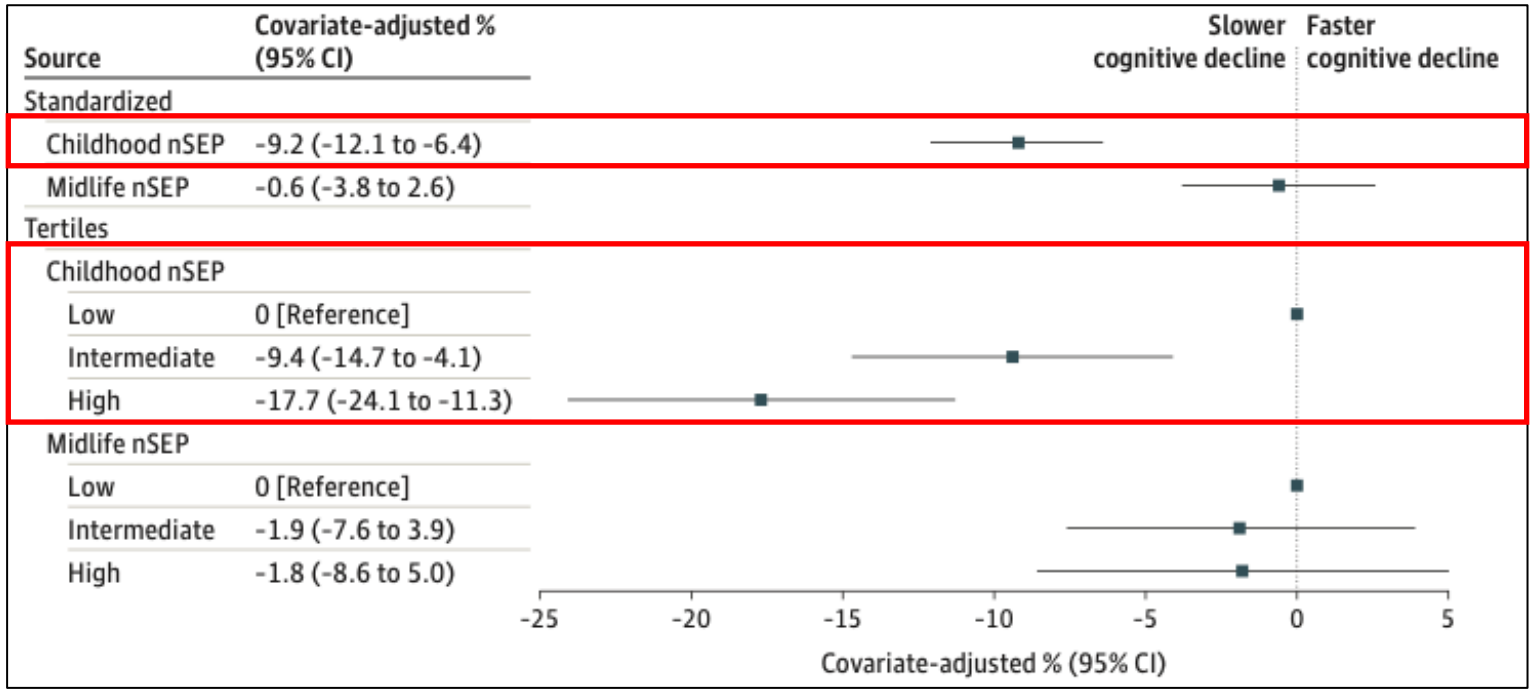
Neighborhood Influences

Quality of education

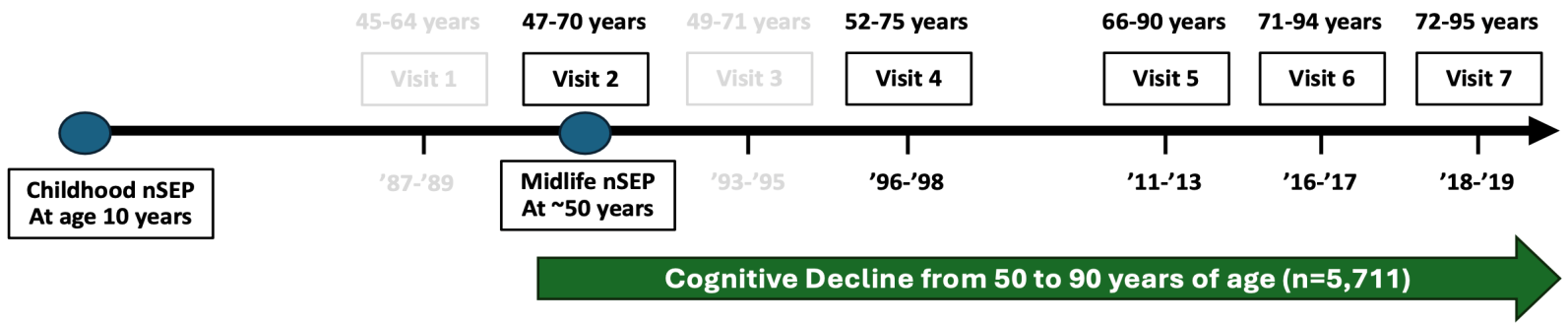
Geography

Livingston et al. 2024 *Lancet*

Early Childhood Experiences are Associated with Cognitive Decline

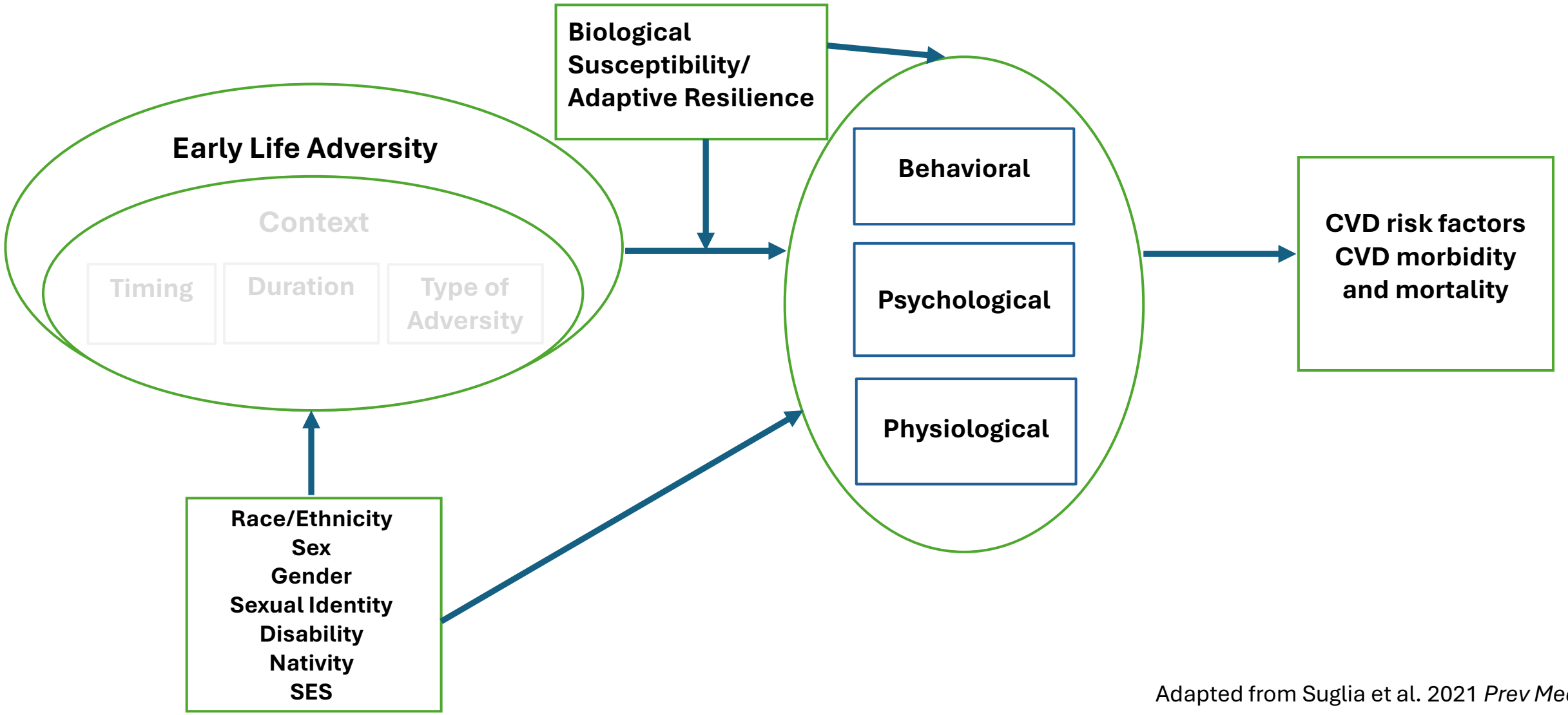


N=5,711
40% men, 23% Black
Median cognitive decline: -0.33 SDs



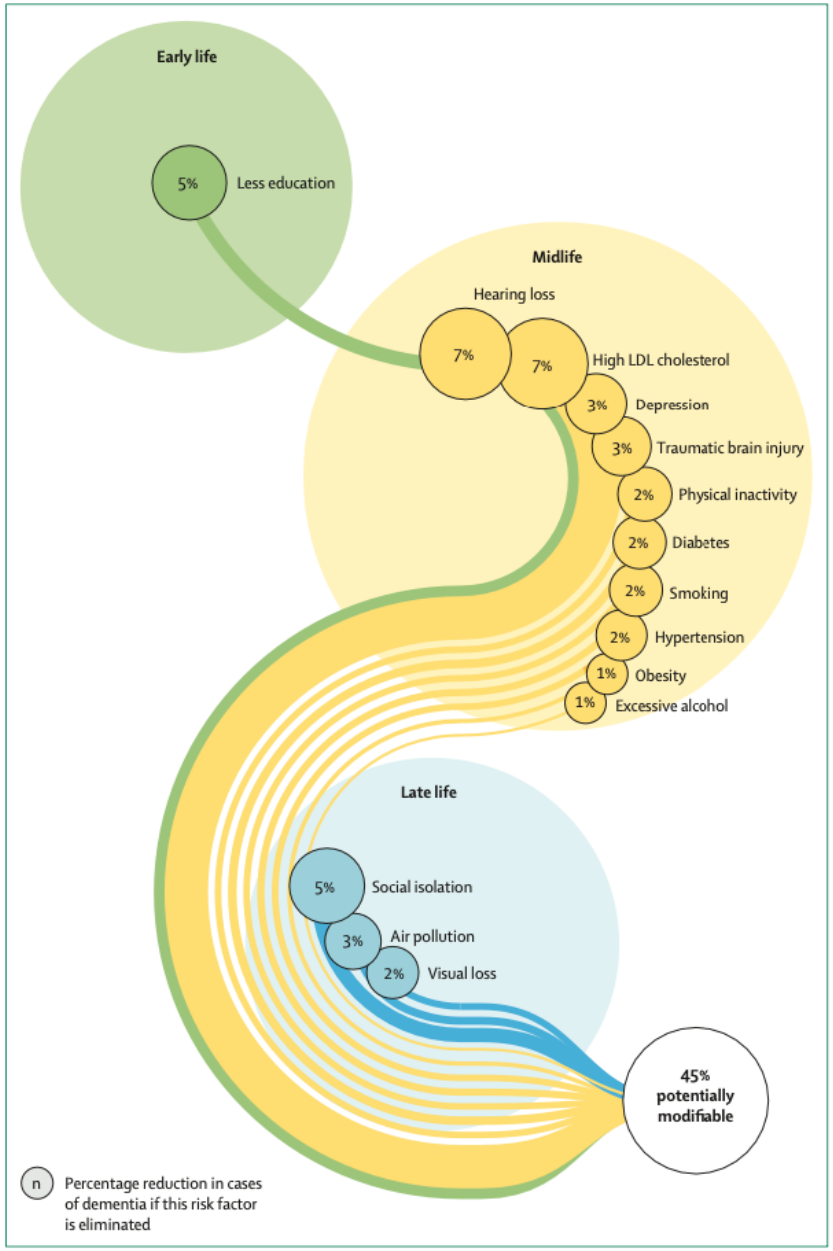
Kucharska-Newton,..., Palta. 2023 *JAMA Netw Open*

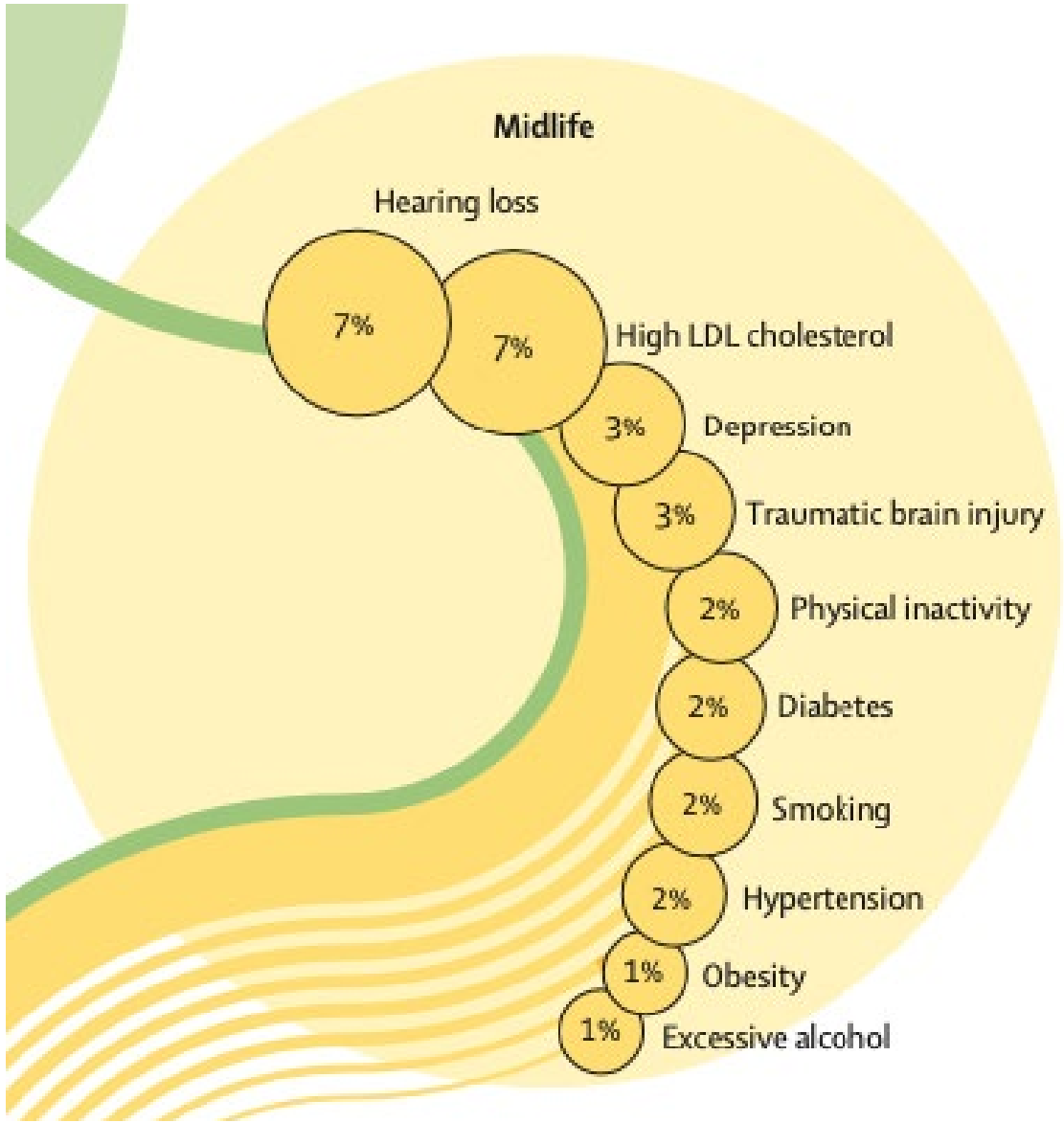
Early Life Factors and their Role in Cardiometabolic Disease Risk



Adapted from Suglia et al. 2021 *Prev Med*

Early life, **Midlife**, and Late life Modifiable Factors for Dementia





High Cholesterol

Diabetes

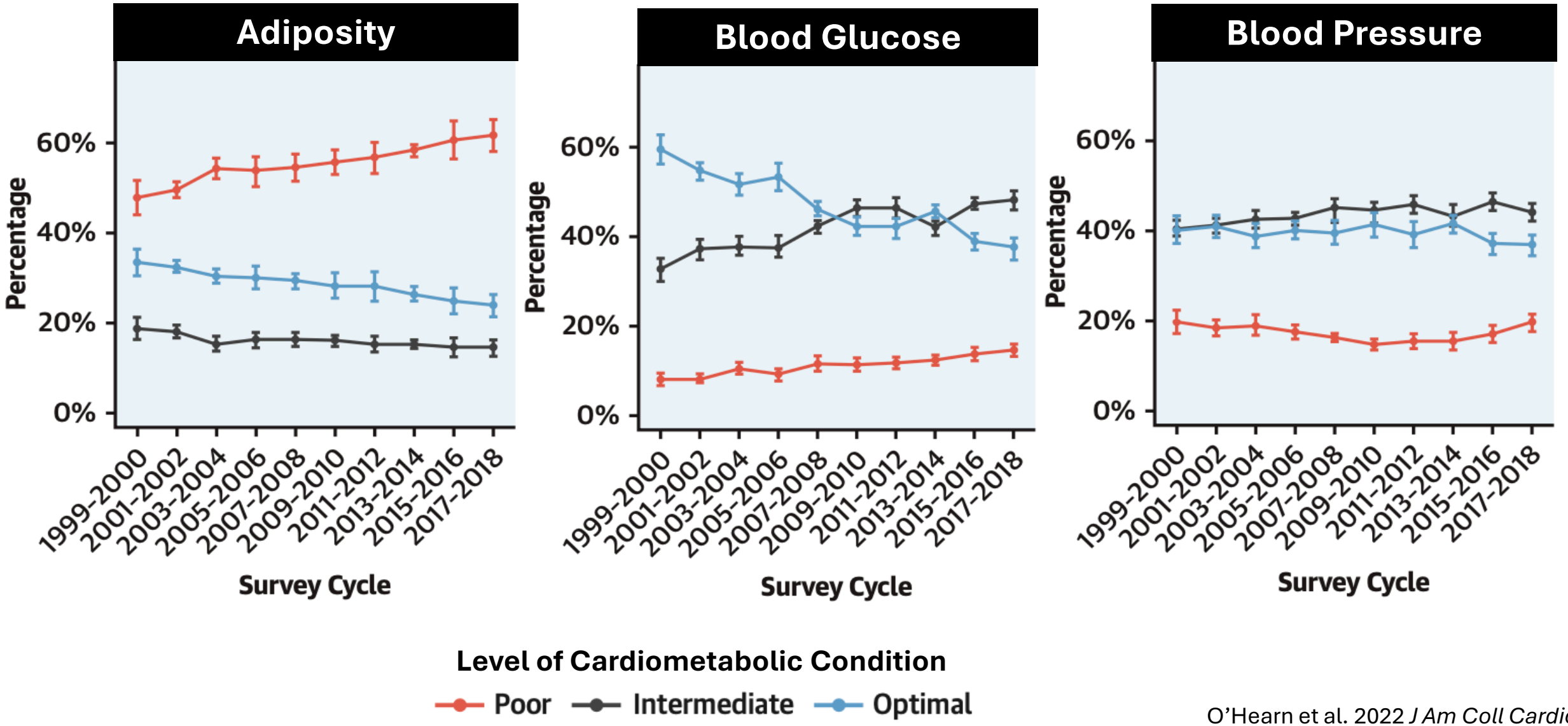
Hypertension

Obesity

Physical Inactivity

Livingston et al. 2024 *Lancet*

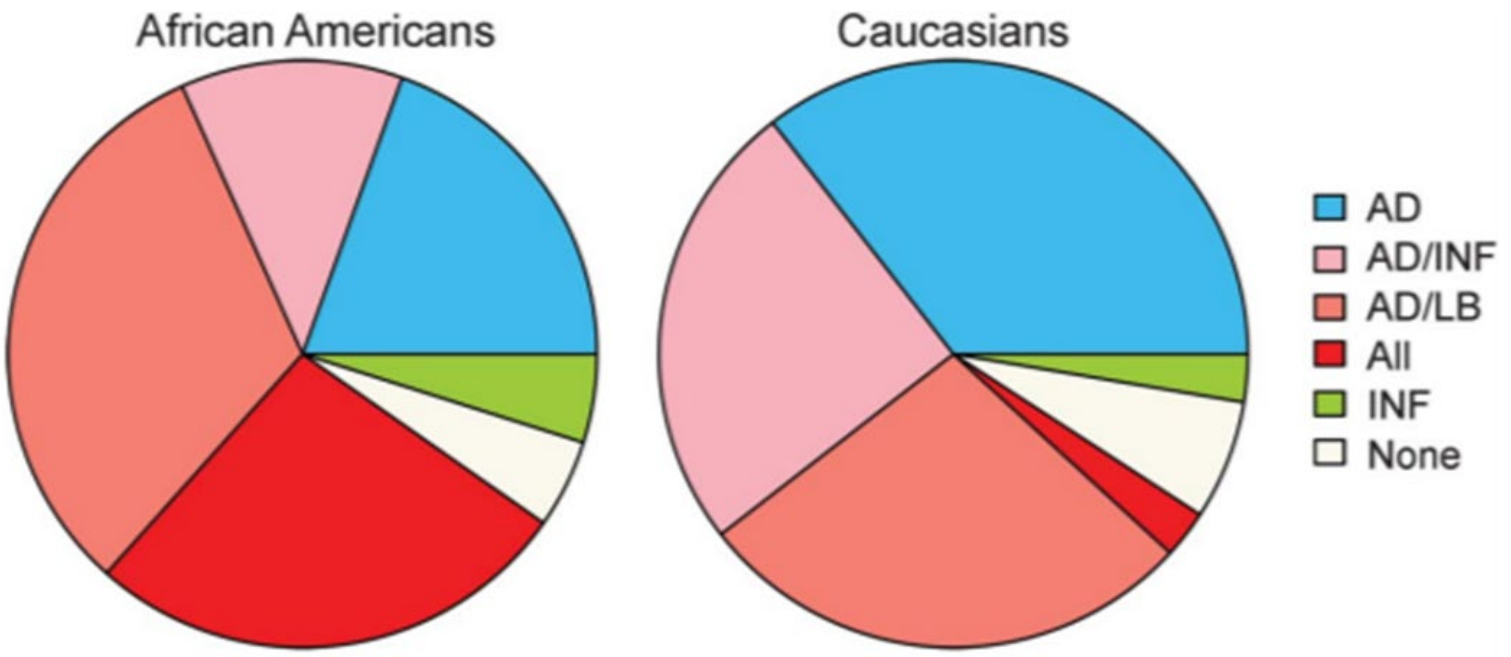
Increasing Prevalence of Cardiometabolic Conditions



O'Hearn et al. 2022 *J Am Coll Cardiol*

Mixed Dementia Etiologies and Vascular Contributions to Cognitive Impairment and Dementia (VCID)

Racial differences in mixed pathology

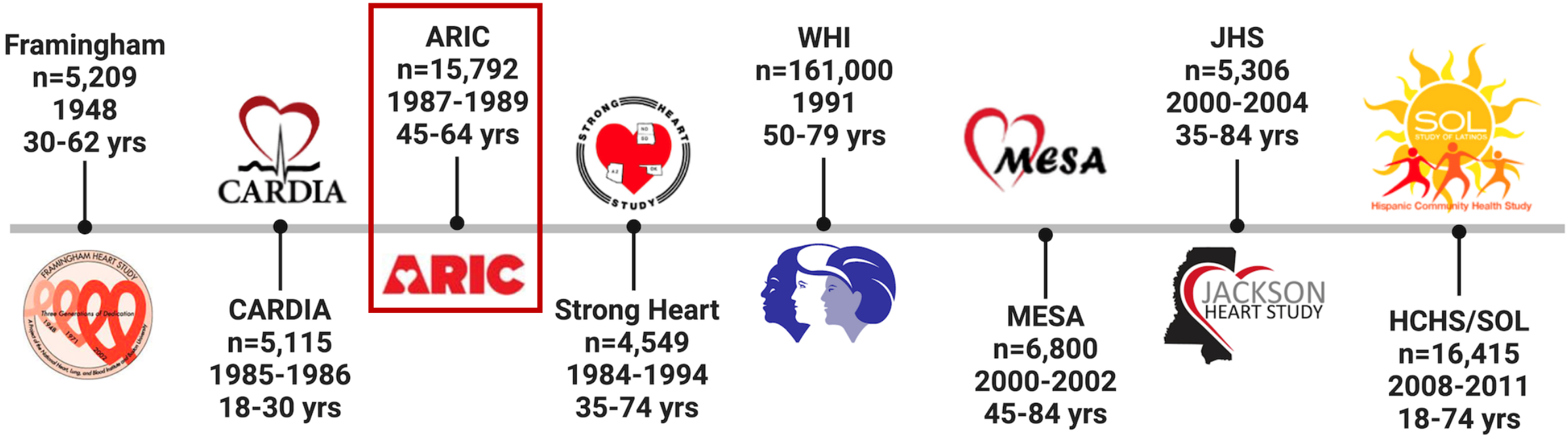


AD: Alzheimer's disease
INF: Infarcts
LB: Lewy bodies

Barnes et al. 2015 *Neurology*

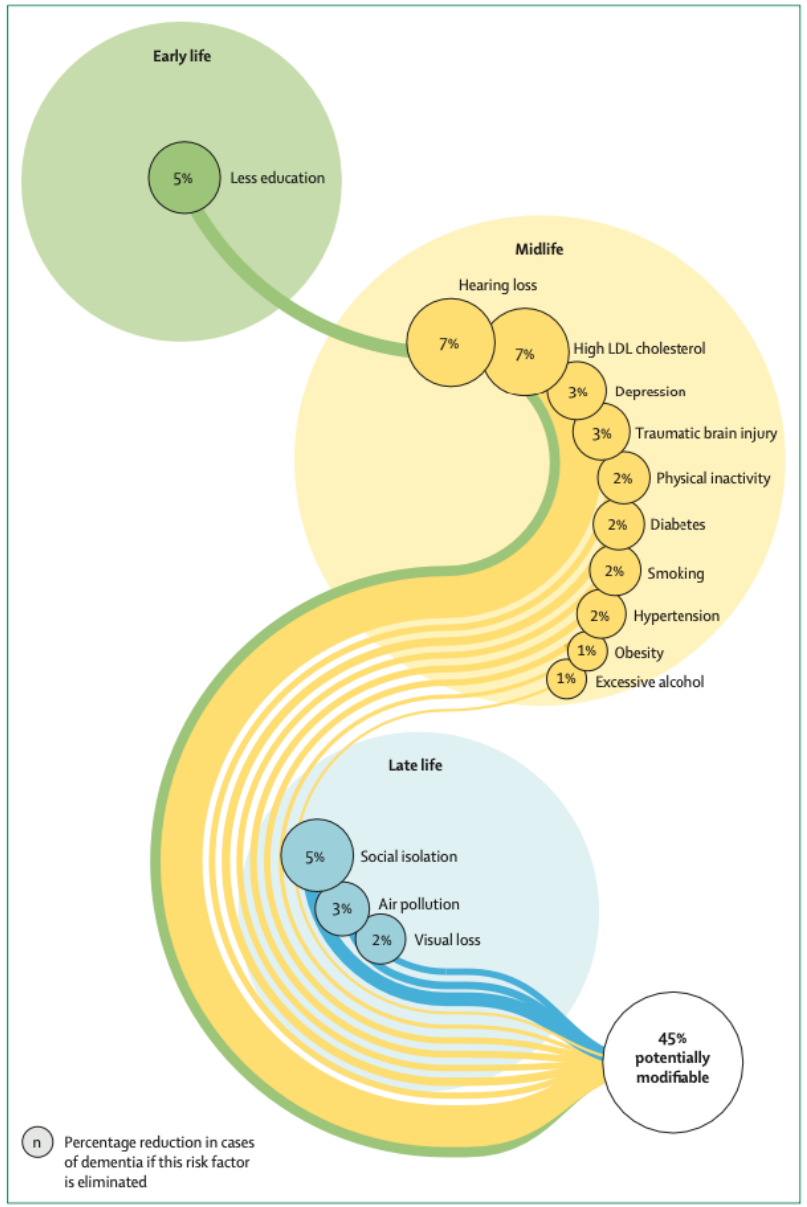
- Cognitive disorders where the primary cause or contributor is vascular disease or vascular injury
- 5-10% of cases are vascular dementia (i.e., infarcts)
- Often co-occurs with Alzheimer's disease

Using Cardiovascular Cohorts to Link Early and Midlife Exposures for Dementia

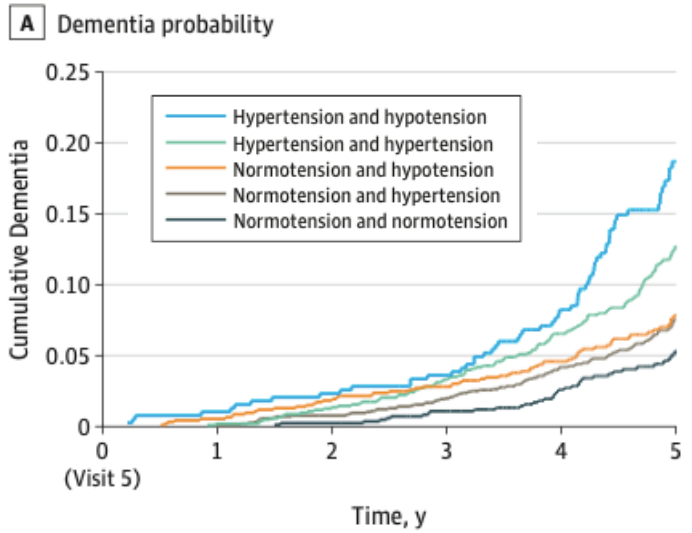


- Designed to investigate etiology of atherosclerosis and CVD
- Examine CVD in young adulthood
- Understand how diseases impact diverse populations
- **Enable the study of vascular contributions to cognitive decline and dementia**

Midlife Vascular Risk Factors as a Key Pathway from Early Life Exposures to Dementia

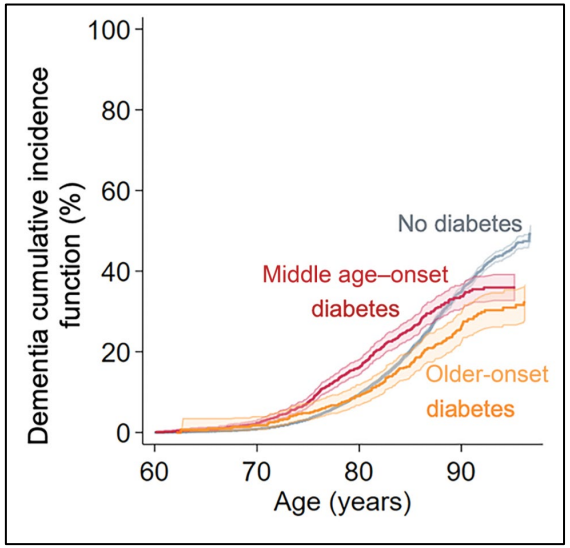


Blood Pressure/ Hypertension



Walker et al. 2019 *JAMA*

Diabetes



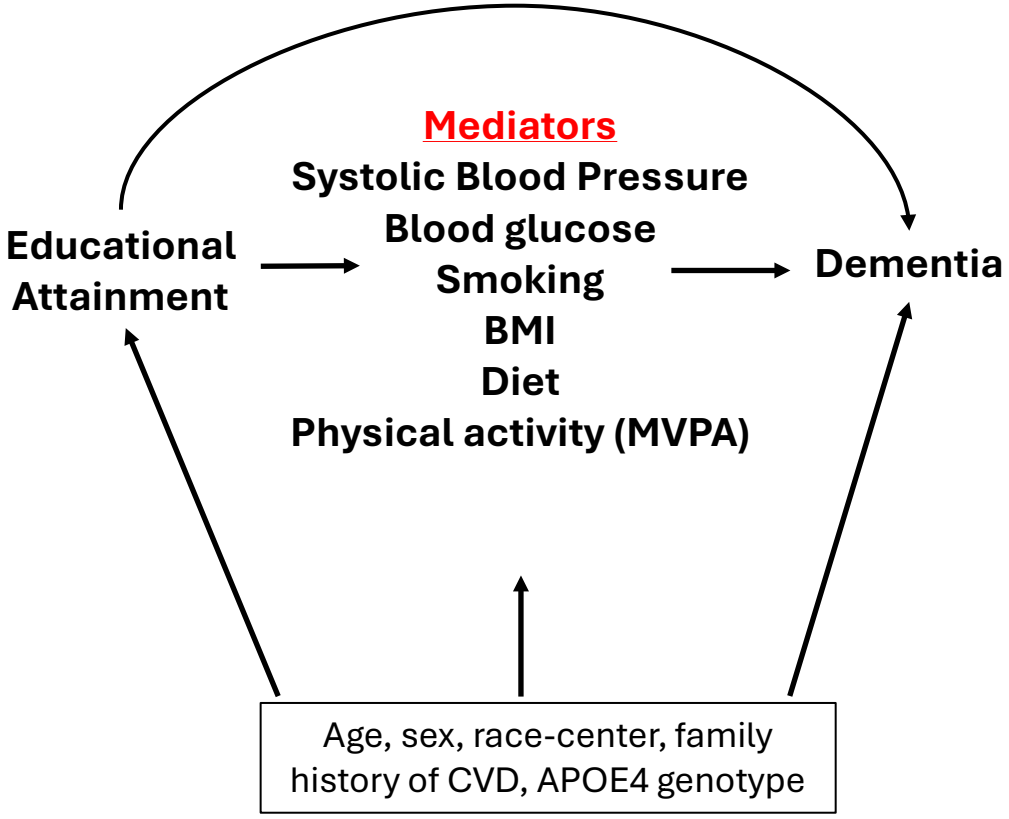
Hu et al. 2024 *Diabetes Care*

Physical Activity

Midlife Physical Activity (PA)	Hazard Ratio of Incident Dementia (95% CI)
No PA	Reference
Low	0.88 (0.75, 1.04)
Middle	**0.77 (0.65, 0.91)**
High	**0.72 (0.61,0.86)**

Palta et al. 2019 *Alzheimers Dement*

Early Life Exposures, Dementia Risk, and Mediation by Midlife Vascular Risk Factors (VRFs)



% Mediation by VRFs only ranged from ~10-26%

	Grade School	HS without Graduation	HS Grad	Some College/ College Grad	Graduate/ Prof School
Total	Ref	10.7%	20.6%	26.1%	24.0%
SBP		2.5%	2.1%	3.5%	5.1%
FBG		2.7%	5.0%	6.6%	6.8%
Smoking		1.1%	6.8%	6.7%	8.4%
BMI		4.5%	1.8%	3.1%	5.1%
Diet		-0.8%	0.8%	0.4%	0.1%
MVPA		0.7%	4.1%	5.8%	-1.6%

Liu et al. 2023 *Ann Neurol*

Cardiovascular Health in Mid- to Late-Life as a Point of Intervention on Past Exposures

SPRINT Systolic Blood Pressure Intervention Trial

Williamson et al. 2019 *JAMA*

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Mean Age: 68 years

Outcomes	Treatment Group: Intensive <120 mmHg — No. With Outcome/Person-Years	Intensive — Cases per 1000 Person-Years	Standard <140 mmHg — No. With Outcome/Person-Years	Standard — Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

Physical Activity

Diet

U.S.POINTER

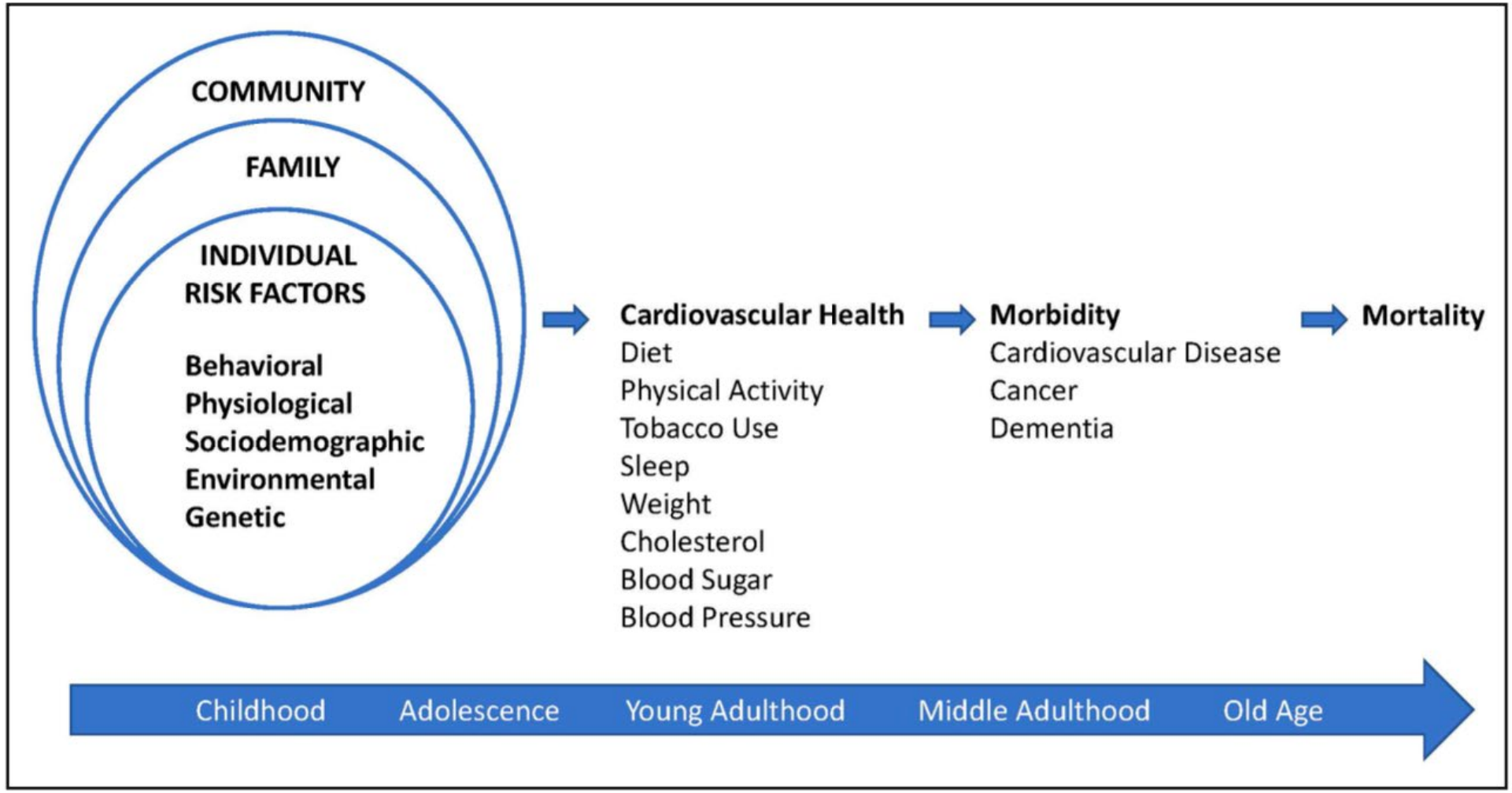
ALZHEIMER'S ASSOCIATION

Baker et al. 2024 *Alzheimers Dement*

Cognitive Stimulation

Vascular Risk Factor Reduction

Even earlier interventions are critical!
But few have done so…



Pedamallu et al. 2023 *Circulation Research*

What do we still need to know?

- Timing and duration of early life disadvantage
  - Gestational period
- Role of midlife vascular risk factors independently and in combination
  (i.e., risk score)
- Current mediation analyses are limited to few SES measures
  (e.g., education, income)
- Moderating role of contextual risk and resilience factors
  - Relationships, community, social support, and other psychosocial impacts
- Associations of early and midlife exposures on dementia subtypes and underlying pathology (i.e., imaging and blood-based biomarkers)

Current Challenges in Cardiovascular Cohort Studies of Dementia

- Limited measures of early life disadvantage
- Potential mismeasurement of relevant modifiable midlife risk factors (e.g., physical activity, occupational exposures, social support)
- Secular trends in cardiometabolic conditions and other comorbidities (i.e., COVID-19) require careful consideration
- Limited racial/ethnic and geographic diversity

Recommendations and Conclusions

- Utilize extant cohorts linked with relevant data resources to better characterize early life disadvantage (e.g., Census linkage)
- Cross-cohort harmonization to enhance racial/ethnic and geographic diversity
- Integrated lifecourse approach through synthetic cohorts to address age gaps in individual cohort studies
- Culturally tailored individual and multilevel interventions for cardiovascular health in children and adolescents

Thank you!

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