

Midlife mediators and modifiers of early-life risk and protective factors

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Disclosures

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Presentation outline

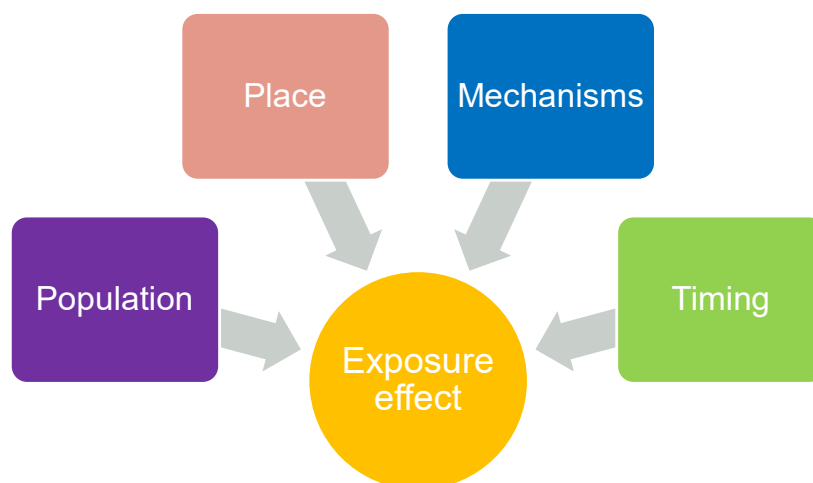
1. Lifecourse models
2. Education
3. Place
4. Data challenges

Specificity matters



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The Who, Where, When, & How Matter



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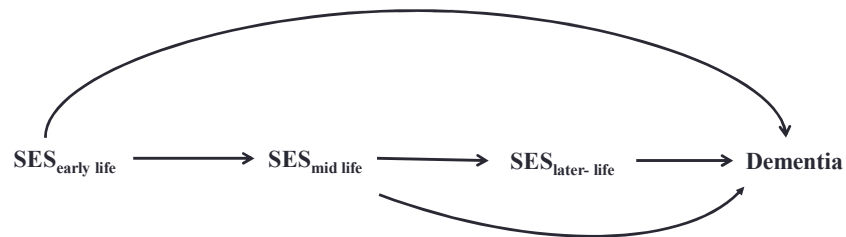
Lifecourse perspective and dementia

- Changes in the brain may occur decades prior to a dementia diagnosis
- **Direct effect:** Early-life exposures impact brain development affecting late-life cognition
- **Indirect effect:** Early-life exposures affect adult and late-life circumstances, which in turn affect late-life cognition



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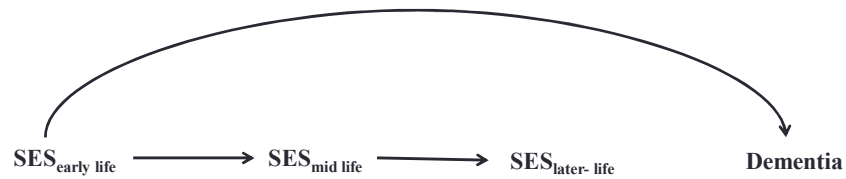
Common lifecourse models: Accumulation model



SES=socioeconomic status

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Common lifecourse models: Early-life critical period model



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Common lifecourse models: Pathway model

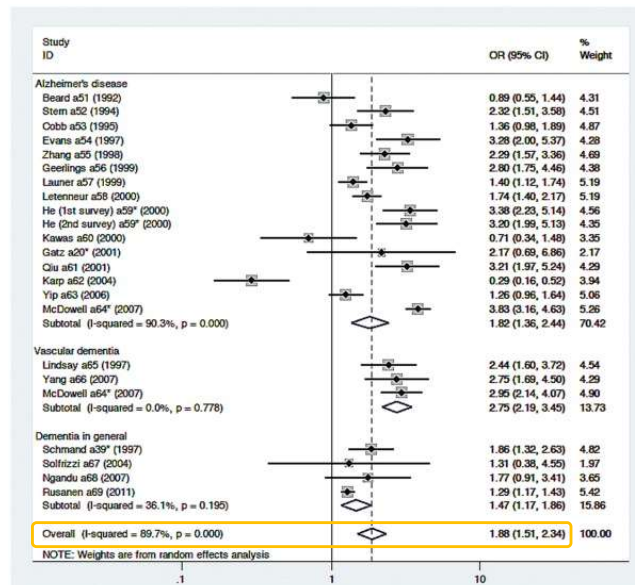


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EDUCATION

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Association between education and dementia incidence



(Meng and D'Arcy, 2012)

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DOI: 10.1002/alz.13038

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION**Association of primary lifetime occupational cognitive complexity and cognitive decline in a diverse cohort: Results from the KHANDLE study**

Yenee Soh, ScD

(Soh et al, 2023)

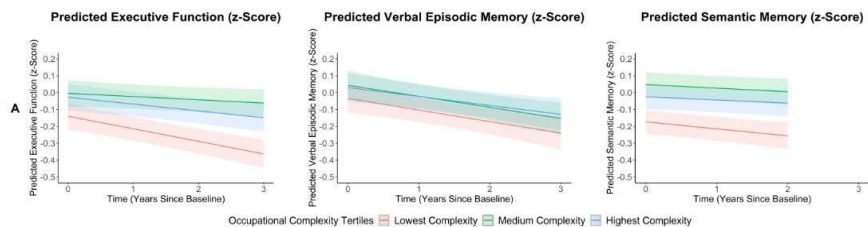
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- More occupational complexity with data associated executive and semantic memory.



(Soh et al, 2023)

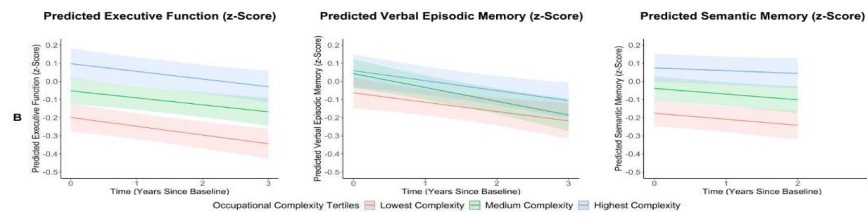
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- More occupational complexity with data was associated with executive and semantic memory
- More occupational complexity with people was associated with executive function, verbal episodic memory, and semantic memory.



(Soh et al, 2023)

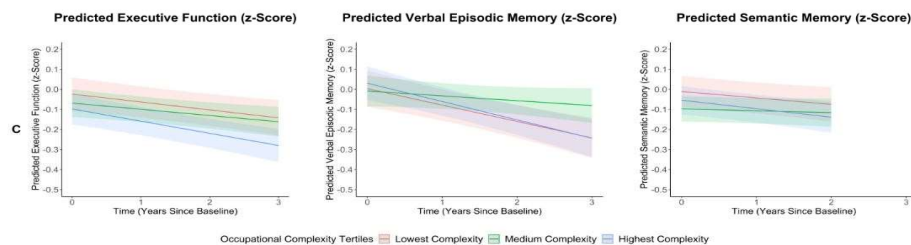
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RESEARCH ARTICLE

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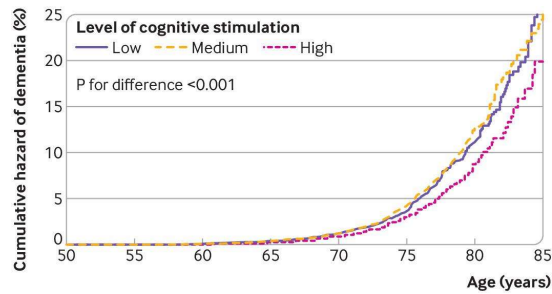
- More occupational complexity with data was associated with executive and semantic memory
- More occupational complexity with people was associated with executive function, verbal episodic memory, and semantic memory.
- No evidence of associations were found for occupational complexity with things and baseline cognition or rate of decline.



(Soh et al, 2023)

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Occupation & Dementia



Cognitive stimulation	No of participants at risk (No with dementia) by age group			
Low	14 797 (32)	16 489 (100)	5528 (181)	557 (43)
Medium	26 743 (53)	29 078 (172)	8577 (280)	777 (63)
High	15 406 (23)	16 863 (71)	4559 (100)	369 (25)

(Kivimaki et al, 2021)

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Education & Occupation

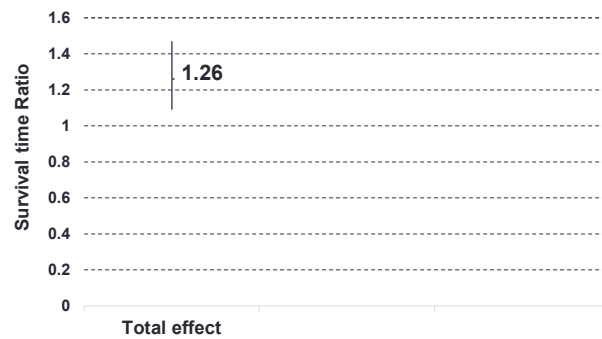
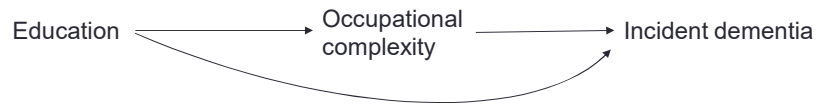
Cognitive stimulation		Total No	Dementia No	Incidence per 10 000 person years	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Education	At work					
Low	Low	55 540	768	8.1		1.00
Low	High	14 005	138	5.9		0.80 (0.66 to 0.97)
High	Low	24 984	162	4.1		0.73 (0.61 to 0.89)
High	High	13 367	75	3.5		0.63 (0.49 to 0.82)

0.5 1 2
Reduced risk Increased risk

(Kivimaki et al, 2021)

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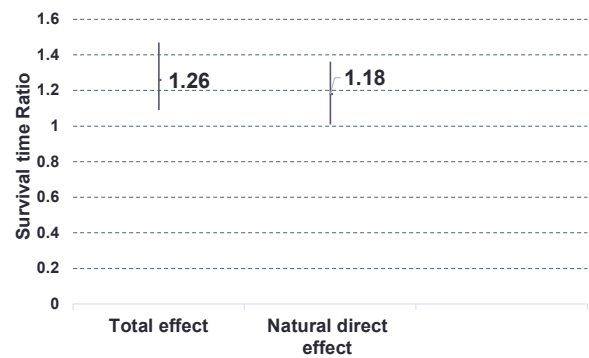
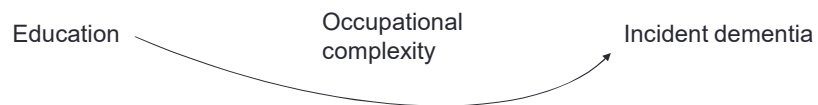
Occupational complexity as mediator



(Hyun et al, 2022)

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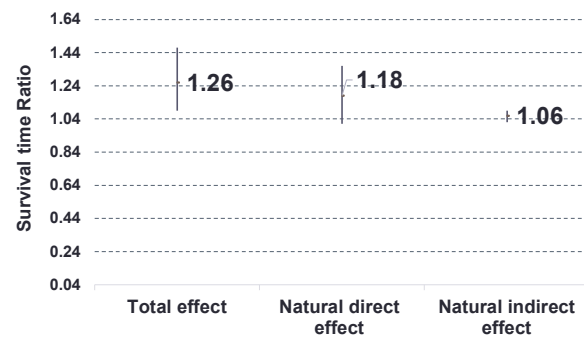
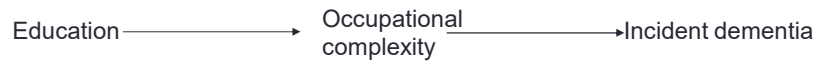
Occupational complexity as mediator



(Hyun et al, 2022)

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Occupational complexity as mediator



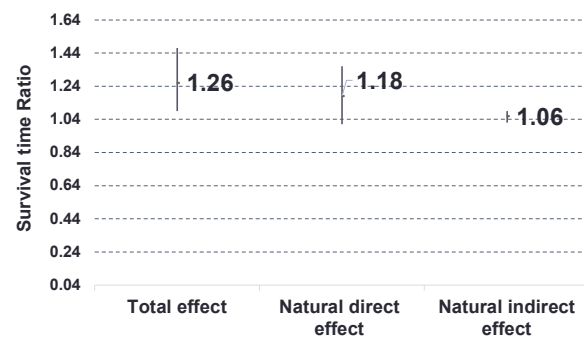
(Hyun et al, 2022)

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Occupational complexity as mediator



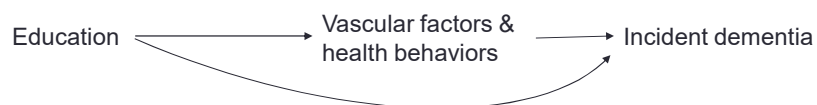
28% mediated



(Hyun et al, 2022)

20

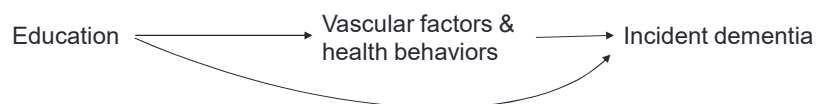
Vascular risk factors & health behaviors as mediators



(Liu et al, 2023)

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Vascular risk factors & health behaviors as mediators



- % mediated by vascular factors: 11% to 25%
- Similar results when include health behavior factors

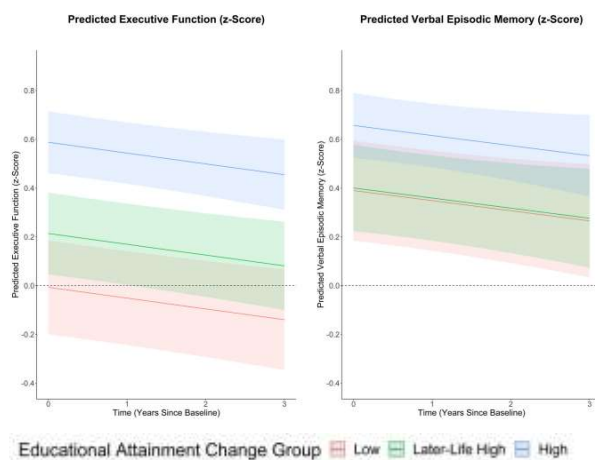
Relevant mechanisms may vary by exposure level

(Liu et al, 2023)

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Timing

- In one's lifecourse



Yenee Soh, ScD

(Soh et al, 2023)

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Timing

- In one's lifecourse
- In history
 - Definition of exposures may change over time
 - Historical and persistent structural biases

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Timing

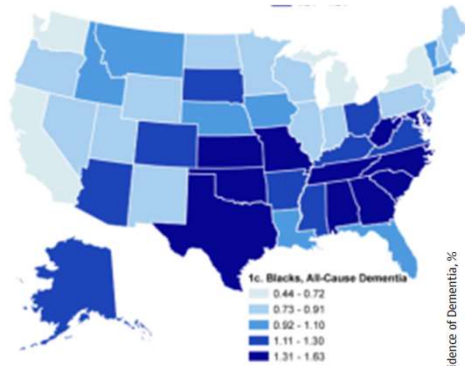
- In one's lifecourse
- In history
 - Definition of exposures may change over time
 - Historical and persistent structural biases
 - For example: legally segregated schools prior to 1954
 - May effect distribution of negative exposure and diminishing returns on the effect protective factors for marginalized population

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PLACE MATTERS

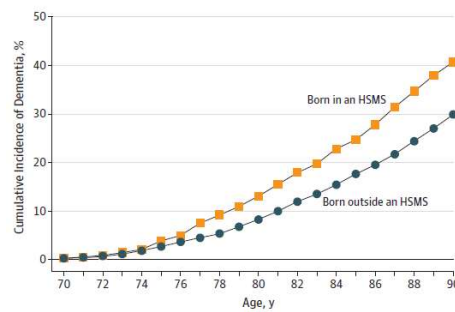
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Birth in the Stroke Belt and Dementia



Odds ratios for all-cause dementia-related mortality in 2000 among Black Adults by birth state compared to the national average (Glymour et al, 2011)

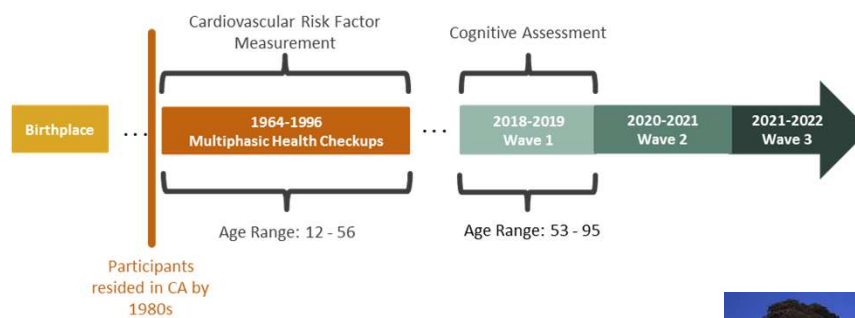
Cumulative incidence of dementia by birth in high stroke mortality state*



*conditional on survival free of dementia until age 65;
HSMS=High stroke mortality state (Gilsanz et al, 2017)

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STAR Study of Healthy Aging in African Americans



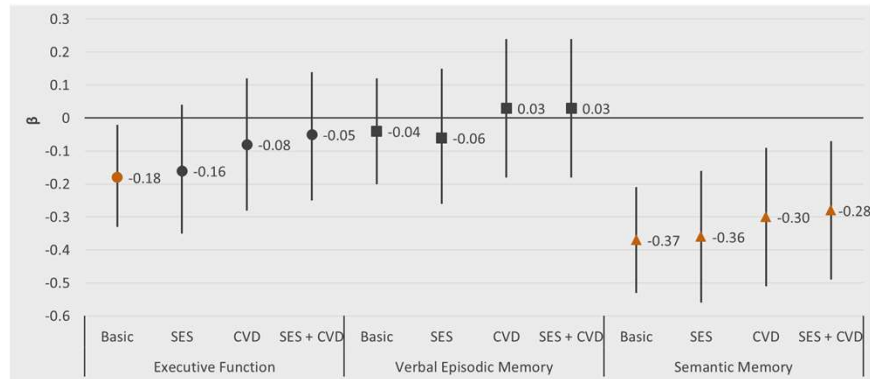
Stroke Belt included: AL, AR, FL, GA, KY, LA, MS, NC, SC, TN, TX



Kristen George, PhD
(George et al, 2021)

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Stroke belt birth state and late-life cognition

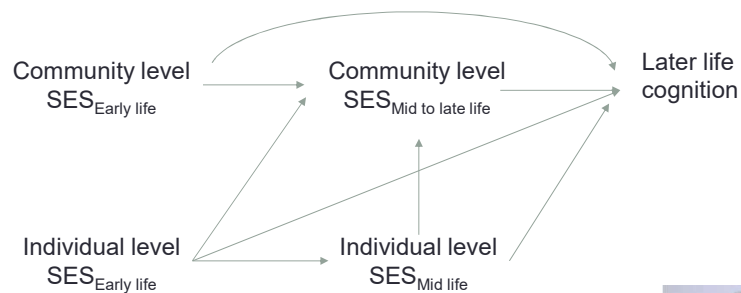


Ref: Born Elsewhere

(George et al, 2021)

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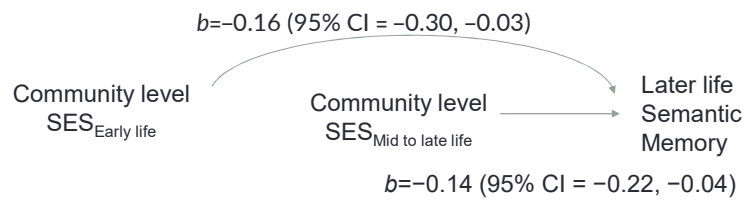
Community level SES



Rachel Peterson, PhD
(Peterson et al, 2023)

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Community level SES



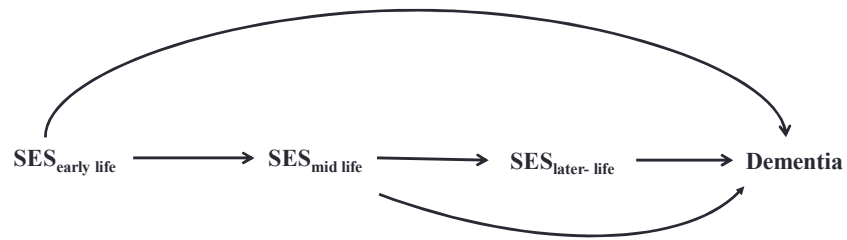
(Peterson et al, 2023)

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METHODOLOGICAL CHALLENGES

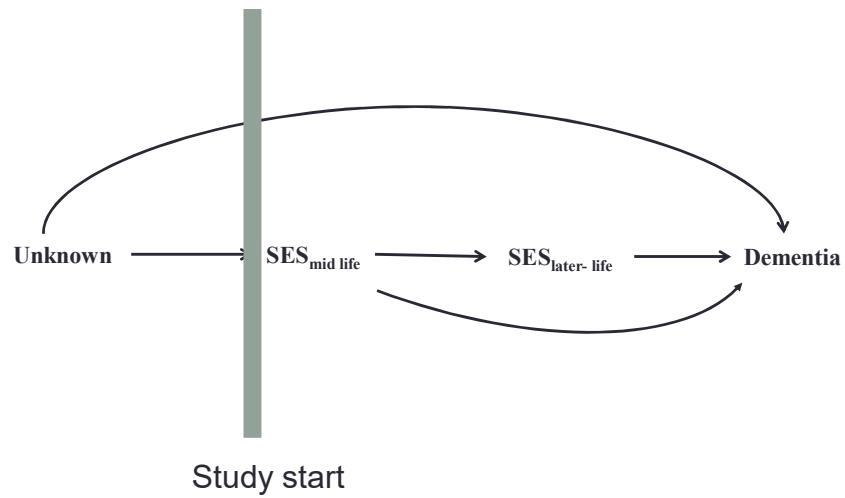
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Accumulation model



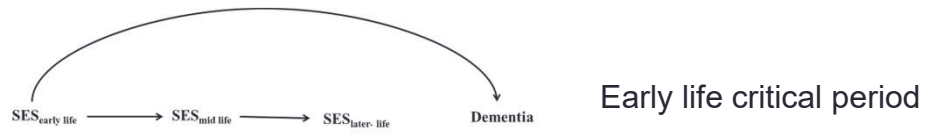
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Late study start bias



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Late study start bias



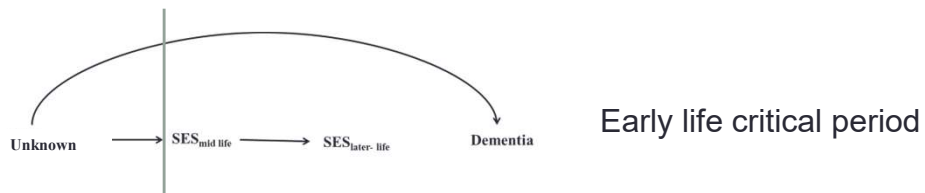
Early life critical period



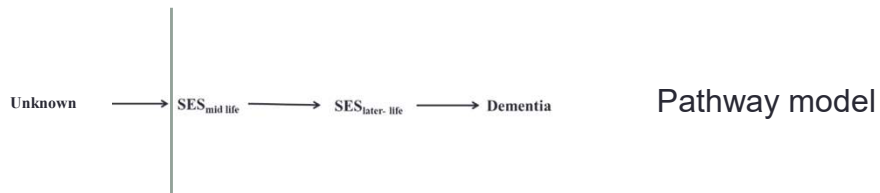
Pathway model

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Late study start bias



Early life critical period



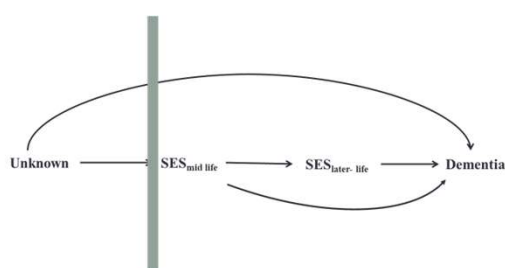
Pathway model

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Underlying causal structure matters

Causal structure=**accumulation**

- Inflated mid- and late-life effects because early life exposure confounds late life exposure
- But mid-and late-life estimates still only partially captured the effects of early-life exposure.
- Simulation: lifetime effect underestimated by 27%



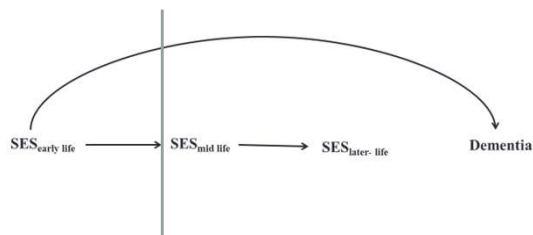
(Gilsanz et al, 2022)

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Underlying causal structure matters

Causal structure= **early life critical period**

- Inflated mid- and late-life effects because early life exposure confounds late life exposure
- But mid-and late-life estimates still only partially captured the effects of early-life exposure.
- Simulation: lifetime effect underestimated by **82%**



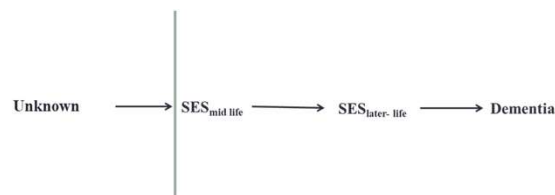
(Gilsanz et al, 2022)

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Underlying causal structure matters

Causal structure=**pathway model**

- Direct effects of mid-and late-life were estimated correctly even in a model without information on early-life exposure
- Simulation: The estimated lifetime effect was minimally biased.

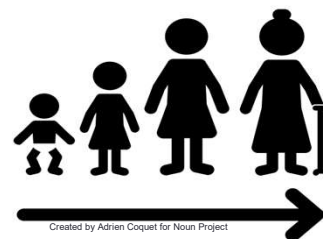


(Gilsanz et al, 2022)

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Study designs

- Birth and early-life cohorts
 - Prospectively collected early life exposures
 - Require a lot of resources (including time)
 - Birth cohort examples: Lothian Birth Cohort 1936, Helsinki Birth Cohort, 946 British national birth cohort study
 - Early-life cohorts: Wisconsin Longitudinal Study (WLS), Project Talent, CARDIA



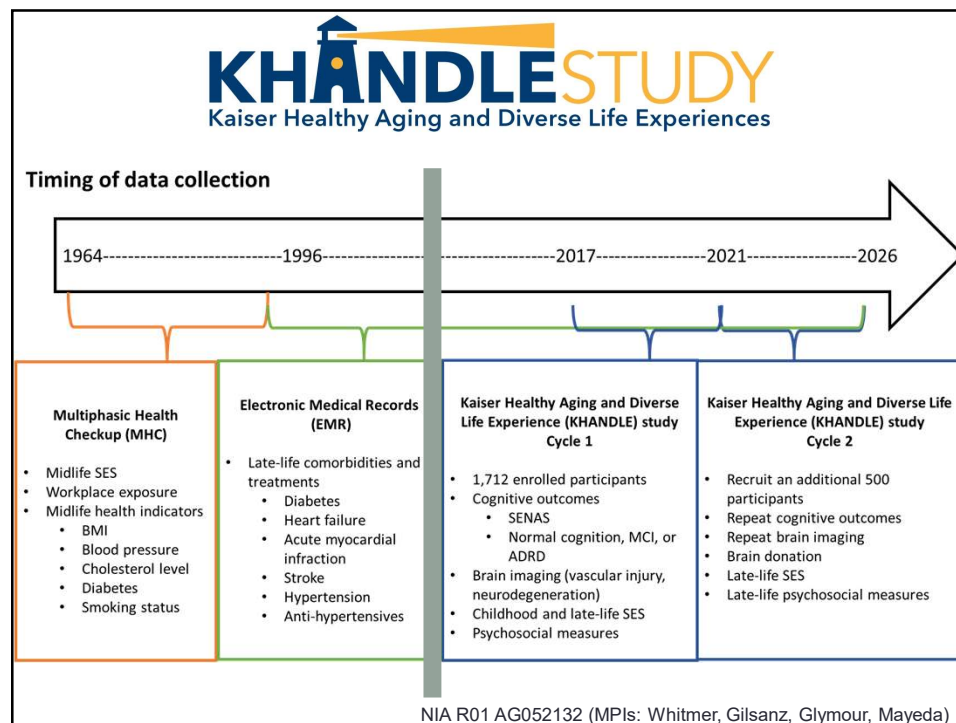
Created by Adrien Coquet for Noun Project

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Study designs

- Birth and earlier life cohorts
- Electronic health records and cohort within integrated health system
 - Prospectively collected data from electronic health records, reduced participant burden, repeated measures
 - Varying follow-up, everyone has health insurance, possible concerns about generalizability and selection bias

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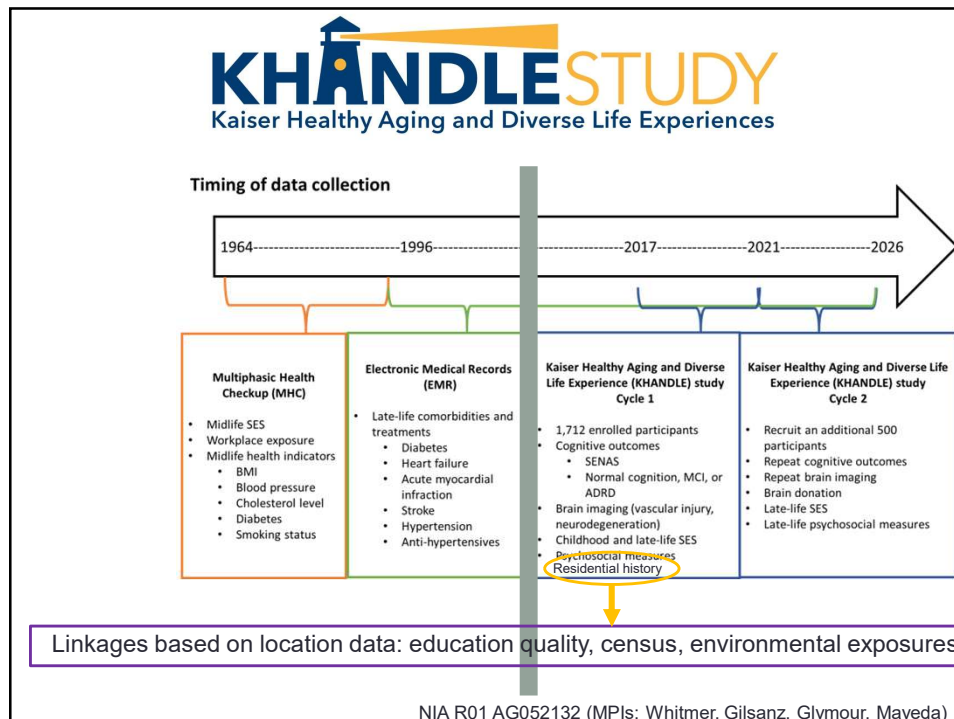
Study designs

- Birth cohorts
- Electronic health records and cohort within integrated health system
- Ask and/or Link
 - About early life exposures
 - About where they lived, worked, and went to school
 - Link to administrative records (e.g. census, education quality, environmental exposures)
 - Concerns about measurement error, selection bias



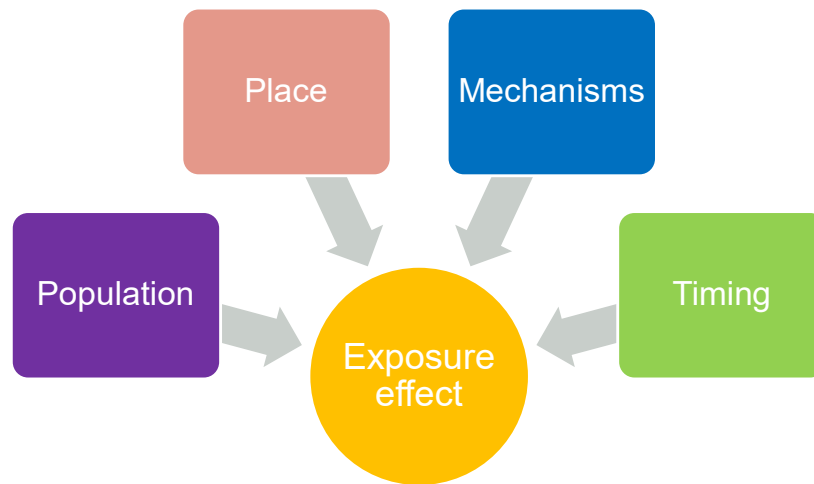
Created by Sharm Fitrout Hayat
from Noun Project

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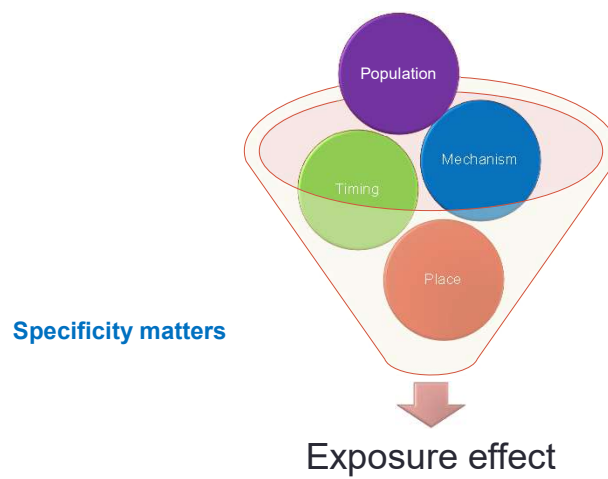
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The Who, Where, When, & How Matter



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The Who, Where, When, & How Matter



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Thank you!

KHANDLE, STAR, & LA90 study participants!

KPNC Division of Research Charles Quesenberry, Molly LaPoint, Yenee Soh, Cognitive Health Research Team members	Funding from NIA: R01AG052132 (MPIs: Whitmer, Gilsanz, Glymour, Mayeda) R01AG050782 (MPIs: Whitmer, Gilsanz) R01AG056519 (MPIs: Whitmer, Gilsanz, Corrada) R01AG066132 (PI: Gilsanz) R01AG067199 (PI: Gilsanz)
UC Davis Rachel Whitmer, Kristen George, Dan Mungas, Charles DeCarli, Brittany Dugger	
Boston University Maria Glymour	
UC Los Angeles Elizabeth Rose Mayeda	
UC Irvine Maria Corrada, Claudia Kawas	
UC San Francisco Tanisha Hill-Jarrett, Marilyn Thomas, Claudia Kawas	
Rush University Lisa Barnes, Crystal Glover	
University of Montana Rachel Peterson	

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