EXPOSOME AS A STRESSOR

October 12, 2022

Overview of the Resilience World – State of the Science

AGS/NIA R13 Bench-to-Bedside Conference Series

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University of Wisconsin School of Medicine and Public Health

FUNDING DISCLOSURES

NIH/National Institute on Aging

NIH/National Institute on Minority Health and Health Disparities

Alzheimer's Association

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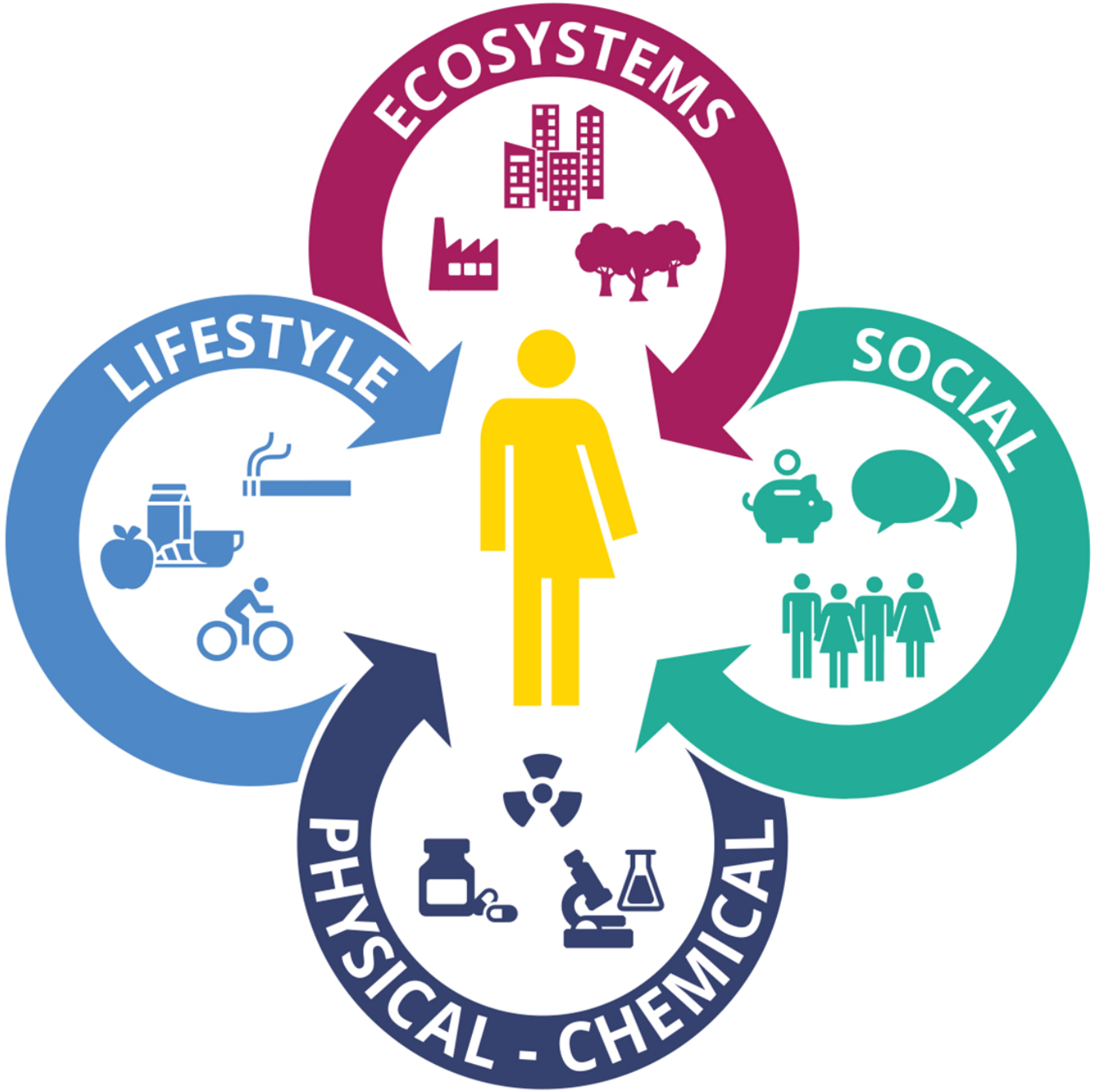
EXPOSOME

The measure of all the exposures of an individual in a lifetime and how those exposures relate to health*

*The National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/niosh/topics/exposome/default.html#:~:text=The%20exposome%20can%20be%20defined,from%20environmental%20and%20occupational%20sources.. Accessed 4/20/2021

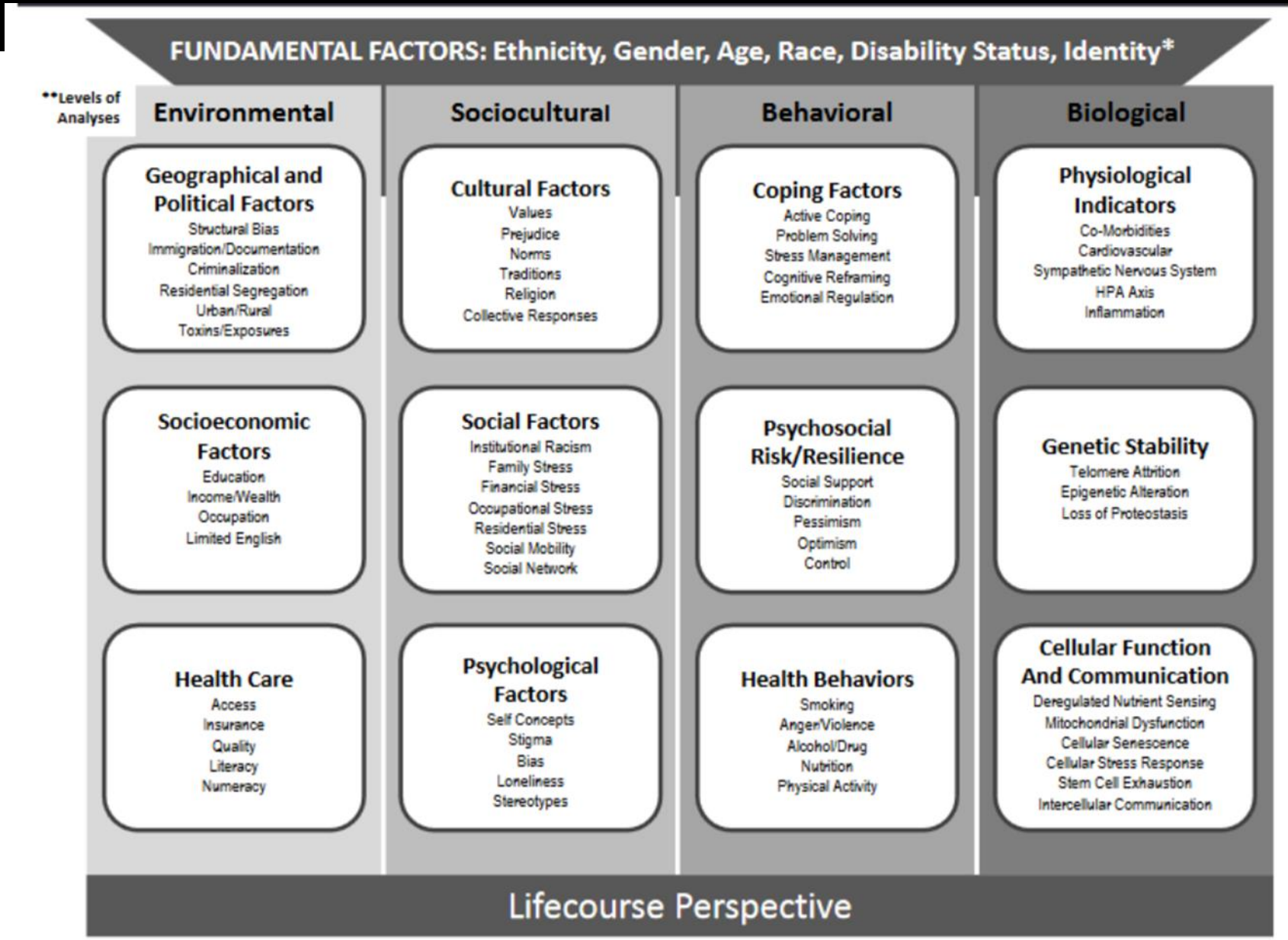
Exposome

- Factors external to the biological individual
- Diverse factors ranging from microbiome to structural inequity



Science. 2020. 367(6476): 392–396.

NIA HEALTH DISPARITIES FRAMEWORK



**Hill, Perez-Stable, Anderson and Bernard, *Ethnicity and Disease*, 2015

NIA HEALTH DISPARITIES FRAMEWORK

ENVIRONMENTAL

SOCIOCULTURAL

BEHAVIORAL

BIOLOGICAL

LIFE COURSE

**Hill, Perez-Stable, Anderson and Bernard, *Ethnicity and Disease*, 2015

SOCIAL DETERMINANTS OF HEALTH

Conditions in the environments in which people are born, live, work, play, worship, and age that impact a wide array of health, functioning, quality-of-life outcomes and risks*

*Office of Disease Prevention and Health Promotion. Healthy People 2020: Social Determinants of Health. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health. Accessed 10/5/2018

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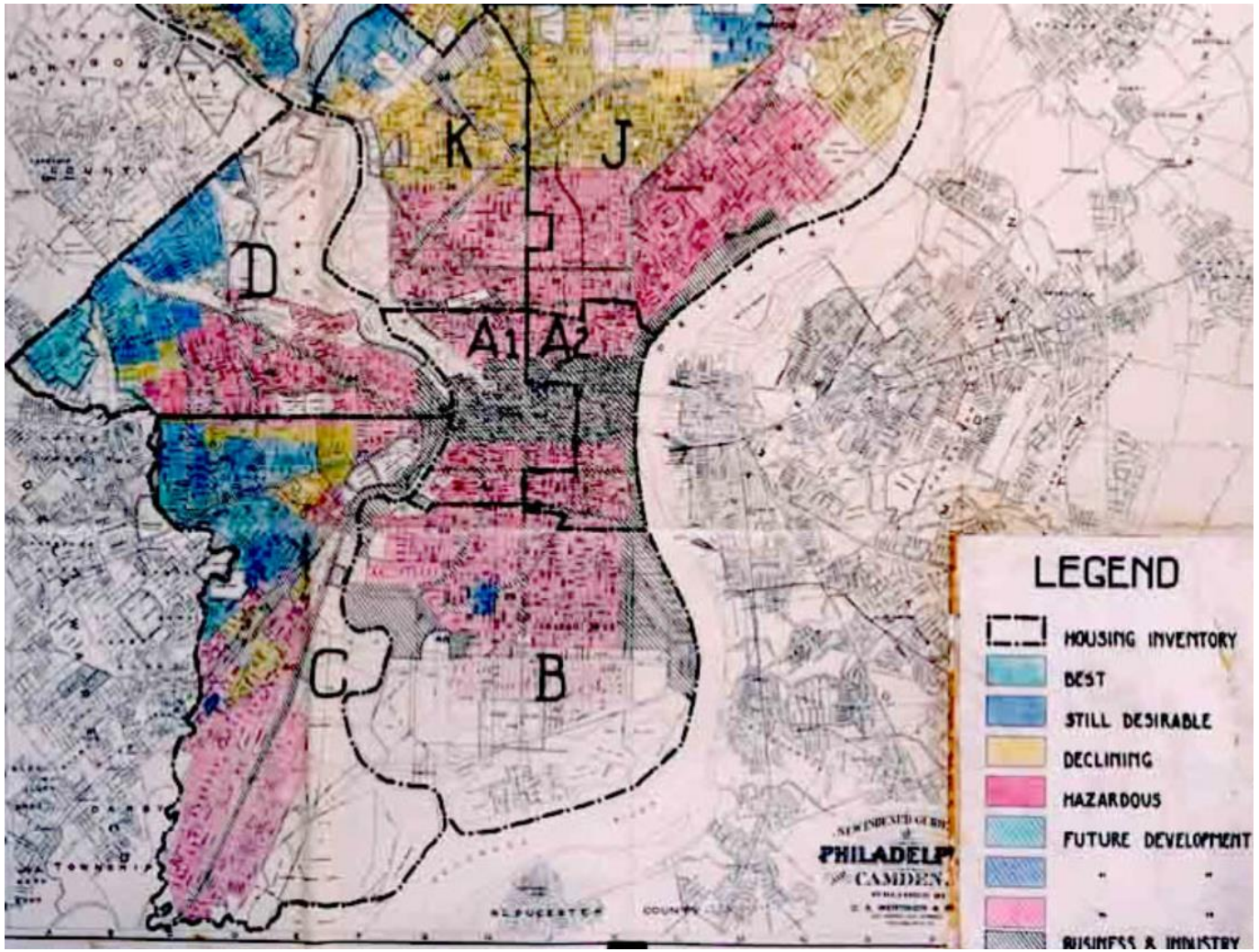
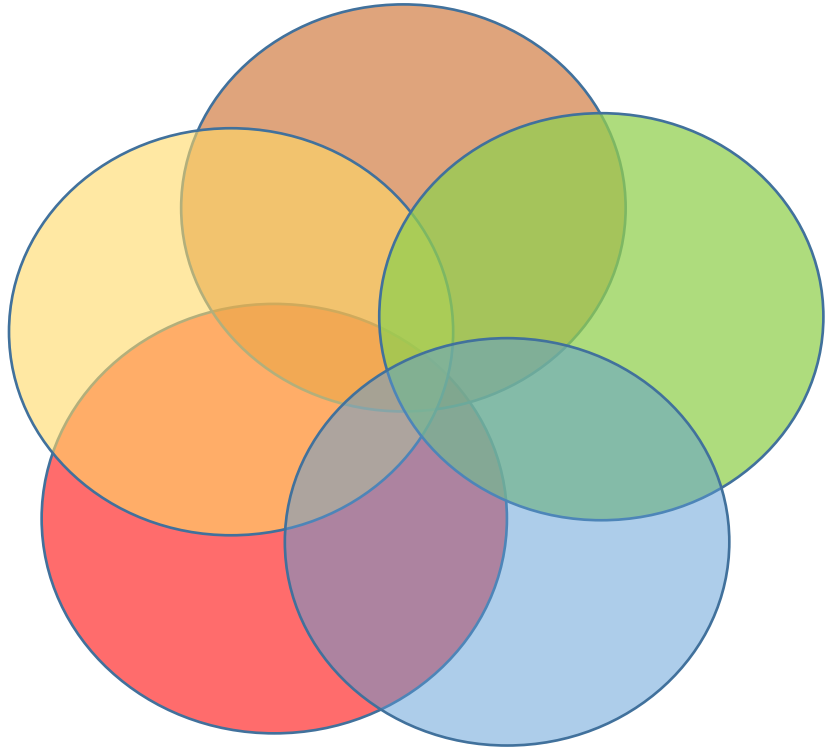
STRUCTURAL INEQUITIES LINK TO EXPOSOME



*The HOLC maps are part of the records of the FHLBB (RG195) at the National Archives II Archived 2016-10-11 at the Wayback Machine.

NIH HEALTH DISPARITIES PRIORITY POPULATIONS

- Hispanics/Latinos
- American Indians/Alaskan Natives
- Blacks/African Americans
- Asian Americans
- Native Hawaiians and Other Pacific Islanders
- Socioeconomically Disadvantaged Populations
- Rural Populations
- Disability Populations
- Sexual and Gender Minorities
- Others



Intersectionality

**Hill, Perez-Stable, Anderson and Bernard, *Ethnicity and Disease*, 2015; https://www.nia.nih.gov/research/osp/framework

EXAMINING THE EXPOSOME

1. Quantifying exposures

2. Linking exposome to biology

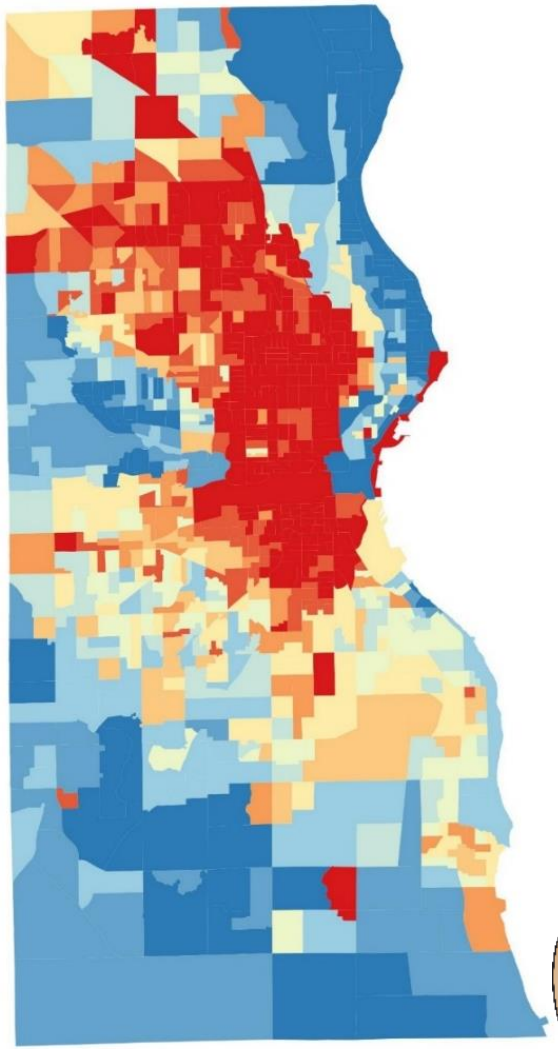
EXAMINING THE EXPOSOME

1. Quantifying exposures

- Rigor, reproducibility, validity, generalizability, harmonizability
- Single time point (easier)
- Life course aligned (harder)

EXAMPLE: QUANTIFYING EXPOSOME USING THE AREA DEPRIVATION INDEX (ADI)*

- ADI construction
  - 17 measures of social determinants of health across small, population sensitive areas
  - Ranked score
  - Time concordant
- Current ADI measures for full US available through the Neighborhood Atlas®*
- Similar metrics available in most countries
- “Microtargeting”



Milwaukee County

*Kind and Buckingham, *New England Journal of Medicine*, 2018

JAMA Network Open

Original Investigation | Surgery

Analysis of Delayed Surgical Treatment and Oncologic Outcomes in Clinical Stage I Non–Small Cell Lung Cancer

Brendan T. Heiden, MD; Daniel B. Eaton Jr, MPH; Kathryn E. Engelhardt, MD, MS; Su-Hsin Chang, PhD, SM; Yan Yan, MD, PhD; Mayank R. Patel, MD; Daniel Kreisel, MD, PhD; Ruben G. Nava, MD; Bryan F. Meyers, MD, MPH; Benjamin D. Kozower, MD, MPH; Varun Puri, MD, MSCI

nd, Roee Gutman, Kristina Monteiro, William R. Buckingham,

DOI: 10.1377/hlthaff.2017.1509
HEALTH AFFAIRS 37,
NO. 7 (2018): –

Rachel Marsh[1] a

Area Deprivation Index Predicts Readmission Risk at an Urban Teaching Hospital

American Journal of Transplantation | AST American Society of Transplantation | ASTS

ORIGINAL ARTICLE

Neighborhood socioeconomic deprivation is associated with worse patient and graft survival following pediatric liver transplantation

Sharad I. Wadhwani, Andrew F. Beck, John Bucuvalas, Laura Gottlieb, Uma Kotagal, Jennifer C. Lai

nuary 2020 | https://doi.org/10.1111/ajt.15786 | Citations: 4

SPECIAL ISSUE: HEA

Neighborhood

JAMA Cardiology | Original Investigation

Association of Socioeconomic Disadvantage With Long-term Mortality After Myocardial Infarction
The Mass General Brigham YOUNG-MI Registry

Adam N. Berman, MD; David W. Biery, AB; Curtis Ginder, MD; Avinainder Singh, MBBS, MMSc; Jonggyu Baek, PhD; Rishi K. Wadhera, MD, MPP, MPhil; Wanda Y. Wu, BA; Sanjay Divakaran, MD; Ersilia M. DeFilippis, MD; Jon Hainer, BS; Christopher P. Cannon, MD; Jorge Plutzky, MD; Donna M. Polk, MD, MPH; Khurram Nasir, MD, MPH; Marcelo F. Di Carli, MD; Arlene S. Ash, PhD; Deepak L. Bhatt, MD, MPH; Ron Blankstein, MD

Annals

LATEST ISSUES

‹ PREV ARTICLE | THIS ISS

ORIGINAL RESEARCH

Safety-Net Hospitals, Under Maryland's All-

Stephen F. Jencks, MD, MPH; Alyson Schu MSPH; Amy J.H. Kind, MD, PhD

Article, Author, and Disclosure Inform

ELSEVIER

Developme Neur | gnitive e

Volume 45, O | 100811

Brain connectivity and socioeconomic status at birth and externalizing symptoms at age 2 years

Bruce Ramphal [a], Diana J. Whalen [b], Jeanette K. Kenley [c], Qiongru Yu [b], Christopher D. Smyser [c, d, e], Cynthia E. Rogers [b, e], Chad M. Sylvester [b]

JAMA Network Open

Original Investigation | Infectious Diseases

Racial Disparities in Incidence and Outcomes Among Patients With COVID-19

L. Silvia Muñoz-Price, MD, PhD; Ann B. Nattinger, MD, MPH; Frida Rivera, MD, PhD; Ryan Hanson, MS; Cameron G. Gmehlin, BA; Adriana Perez, MS; Siddhartha Singh, MD, MS, MBA; Blake W. Buchan, PhD; Nathan A. Ledeboer, PhD; Liliana E. Pezzin, PhD, JD

ACTIONABILITY OF THE EXPOSOME

Ethical Allocation of COVID Therapies

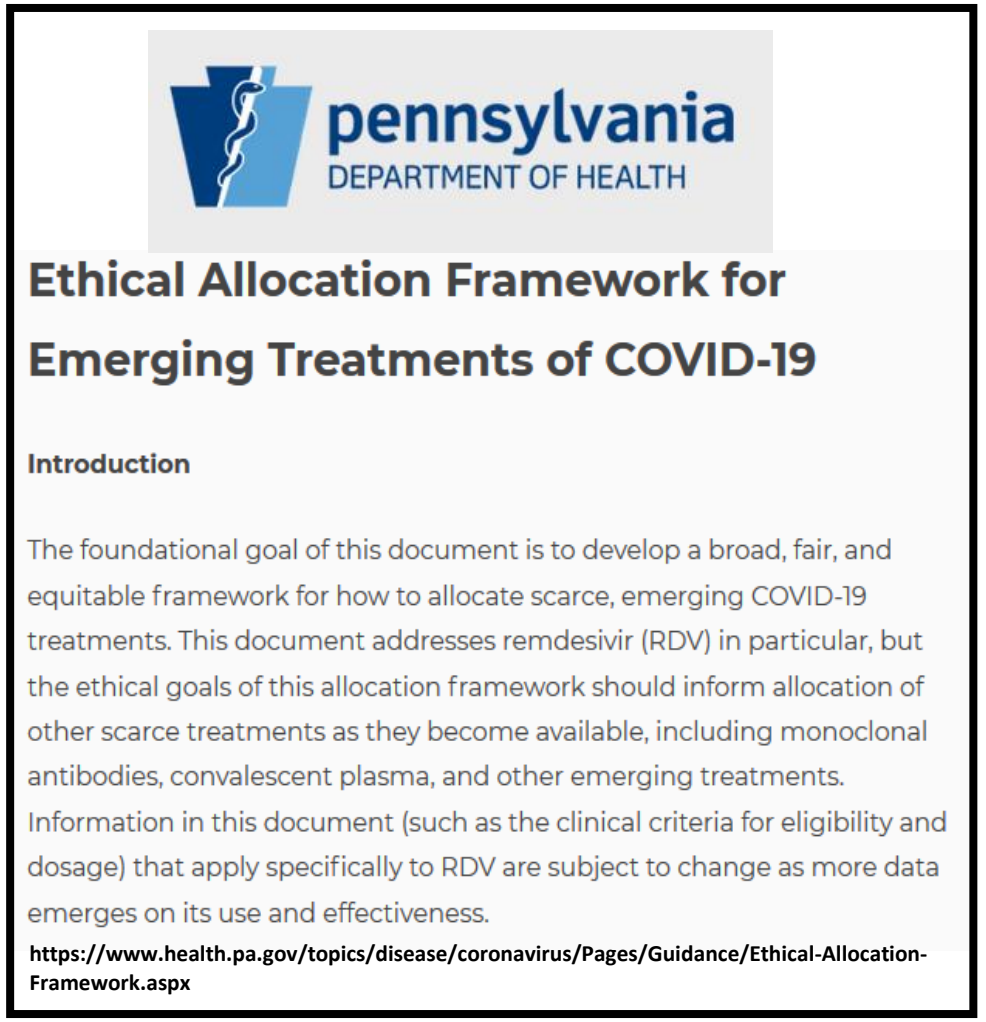
- Example: Pennsylvania

COVID Vaccine Resource Targeting

- Example: Alaska

Efficiently Aligning Health System Resources to Needs

- Example: US Centers for Medicare and Medicaid Services (CMS)
  - 2022 ACO Realizing Equity, Access, and Community Health (REACH) Model



Health Equity Benchmark Adjustment

ACO REACH includes a benchmark adjustment that increases benchmarks for ACOs serving higher proportions of underserved beneficiaries

CMS will stratify all beneficiaries aligned to ACO REACH using a composite measure of underservice that incorporates a combination of[1]:

Area Deprivation Index	Dual Medicaid Status
*Area-level measure of **local socioeconomic factors** correlated with medical disparities and underservice*	*Beneficiary-level measure of economic challenges affecting individuals' ability to access high quality care*
Percentile Score from 1-100	**25 Point Adjustment for Full or Partial Dual Eligibility**

91st – 100th Percentile (Top Decile)	***+$30 PBPM Adjustment***
51st – 90th Percentile (Middle 4 Deciles)	*No Adjustment*
1st – 50th Percentile (Bottom 5 Deciles)	*-$6 PBPM Adjustment*

1. CMS may explore other variables to include in this assessment and will notify applicants prior to the start of PY2023 if any other variables are included.

*2022 ACO Realizing Equity, Access, and Community Health (REACH) Model [https://innovation.cms.gov/media/document/aco-reach-fin-meth-webinar-slides}

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

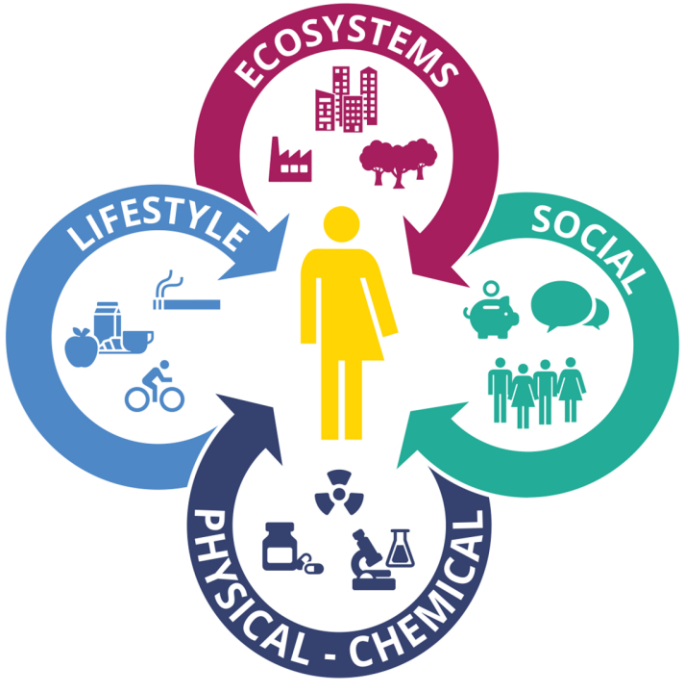
EXAMINING THE EXPOSOME

1. Quantifying exposures

2. Linking exposome to biology

SOCIAL-BIOLOGICAL PHENOTYPING

- Facilitate mechanistic health disparities research
- Link exposures to biological process
- Expand the potential of existing programs in completely new ways



Exposome

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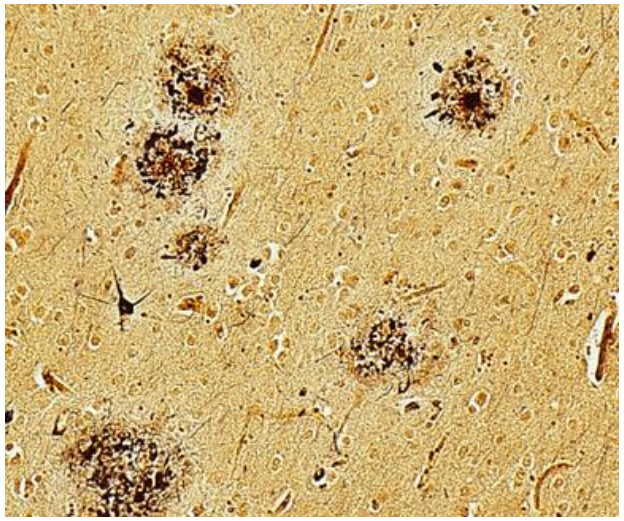
EXAMINING THE EXPOSOME

1. Quantifying exposures

2. Linking exposome to biology

- Methodological considerations
- Infrastructure (technical, legal, administrative)
- Multi-disciplinary expertise

EXAMPLE: LINKING EXPOSOME TO BIOLOGY



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- N=453 decedents who donated their brain to Wisconsin or University California San Diego ADRC brain banks, 1993-2016
- No social factor characterization available
- Residential address at death geocoded, linked to neighborhood disadvantage by ADI
- Neuropathologic features drawn from National Alzheimer's Coordinating Center and autopsy reports

Powell et al, JAMA-Open, 2020

JAMA Network | Open

Original Investigation | Public Health

Association of Neighborhood-Level Disadvantage With Alzheimer Disease Neuropathology

W. Ryan Powell, PhD; William R. Buckingham, PhD; Jamie L. Larson, PhD; Leigha Vilen, BS; Menggang Yu, PhD; M. Shahriar Salamat, MD, PhD; Barbara B. Bendlin, PhD; Robert A. Rissman, PhD; Amy J. H. Kind, MD, PhD

Abstract

IMPORTANCE Social determinants of health, such as income, education, housing quality, and employment, are associated with disparities in Alzheimer disease and health generally, yet these determinants are rarely incorporated within neuropathology research.

OBJECTIVE To establish the feasibility of linking neuropathology data to social determinants of health exposures using neighborhood disadvantage metrics (the validated Area Deprivation Index)

Key Points

Question Can neighborhood disadvantage, a social determinant of health, be incorporated into existing brain bank data to evaluate the risk of biological outcomes, such as Alzheimer disease neuropathology?

Living in the most disadvantaged neighborhood decile was associated increased odds of AD neuropathology

June 11, 2020

EXAMPLE: THE NEIGHBORHOODS STUDY

(R01AG070883; PI KIND, MPI BENDLIN)

Aim 1: Determine the impact of the **cumulative dose and timing** of neighborhood disadvantage exposure (indexed by ADI), on **cognitive function and change** over time

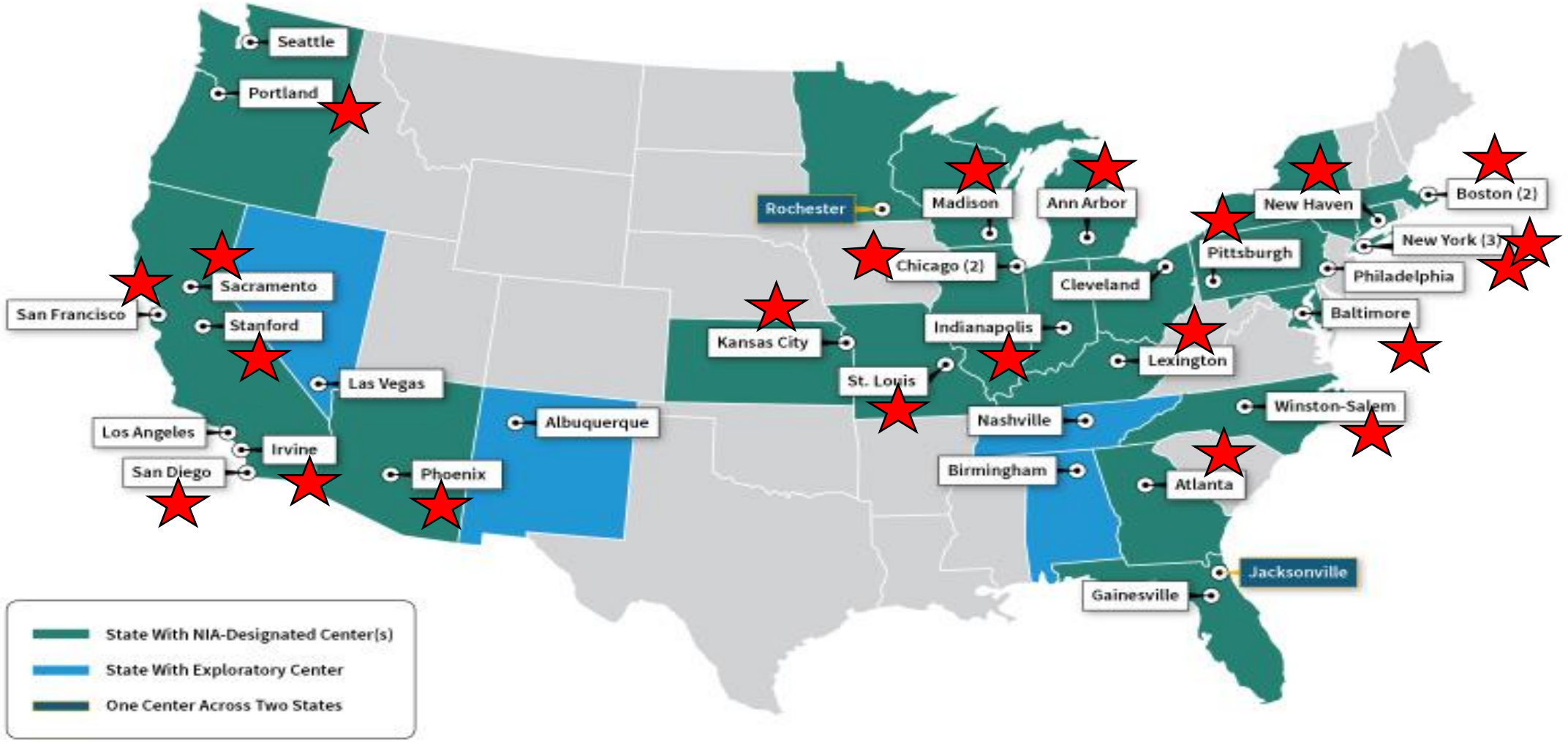
Aim 2: on AD-specific markers indexed by neuroimaging (**amyloid and tau PET**) and the secondary outcomes of vascular burden and volumetric MRI; and

Aim 3: on **neuropathologic tissue features and diagnosis**.

Aim 4: Using existing ADRC data and newly collected survey data, define the extent to which individual race/ethnicity, age, sex, income, education, comorbidity and health-behaviors mediate these relationships.

THE NEIGHBORHOODS STUDY

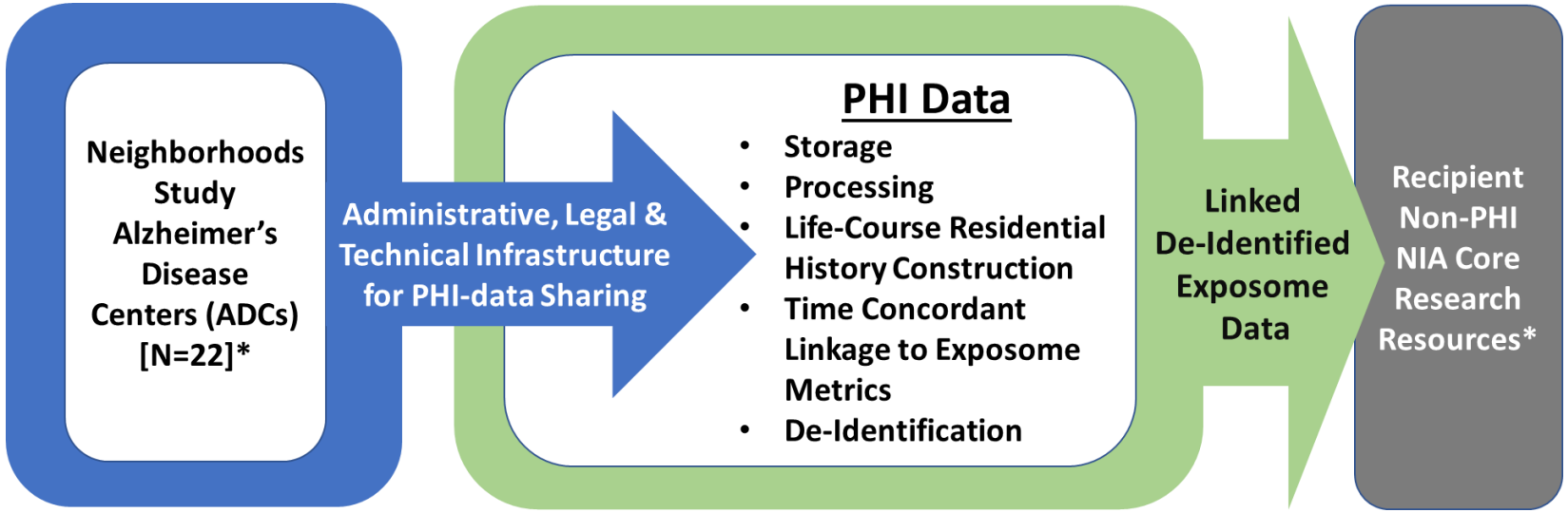
(R01AG070883; PI KIND, MPI BENDLIN)



EXAMPLE: NOVEL ADMINISTRATIVE INFRASTRUCTURE

(R01AG070883; PI KIND, MPI BENDLIN)

- **Multi-site Protected Health Information (PHI)** is required for many disparities aligned life-course exposome assessments
- Requires **high-security, HIPPA compliant administrative, legal and cyber infrastructure**
- **Substantial undertaking**



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EXPOSOME: GAPS AND OPPORTUNITIES

<u>Gap</u>: Exposome Measurement

- Promote development and availability of rigorous, harmonizable life-course aligned exposome measures

<u>Gap</u>: Standardizing Social-Biological Phenotyping

- Develop processes and infrastructure to promote more routine inclusion of exposome in traditional biological-focused assessments
- Increase scientific capacity to perform this work - multi-disciplinary teams

<u>Gap</u>: Health Resilience in Adverse Exposome

- Identifying factors, interventions that promote health in adverse exposome

<u>Many Other Gaps</u>: Exposome as an Emerging Field

ACKNOWLEDGMENTS

ADRC	Participating Components+	Site PI	Site Co-I
University of Wisconsin	BB/CC	Amy Kind/Barb Bendlin (MPI)	Vikas Singh, Menggang Yu
Banner Alzheimer's Institute	BB/CC	Eric Reiman	Thomas Beach, Kewei Chen
Boston University	BB/CC	Maureen O'Connor	Jonathan Jackson
Emory University	BB/CC	Felicia Goldstein	
Indiana University	BB/CC	Shannon Risacher	Andrew Saykin, Liana Apostolova
Johns Hopkins University	BB/CC	Corrine Pettigrew	
Mount Sinai	BB/CC	Mary Sano	Carolyn Zhu, Judith Neugroschi
New York University	BB/CC	Josh Chodosh, Thomas Wisniewski	Karyn Marsh
Oregon Health & Science University	BB/CC	Aimee Pierce	Randall Woltjer, Raina Croff
Rush University	BB only	Melissa Lamar	David Bennett, Lisa Barnes
Stanford University	BB/CC	Victor Henderson	
UC-Davis*	BB/CC	Oanh Meyer	Rachel Whitmer, Sarah Farias
UC-Irvine	BB/CC	David Sultzer	
UC-San Diego	BB/CC	Robert Rissman	James Brewer
UC-San Francisco	BB/CC	Bruce Miller	Serggio Lanata
University of Kansas	BB/CC	Jonathan Mahnken	Jill Morris, Rebecca Lepping
University of Kentucky	BB only	Erin Abner	Anna Kucharska-Newton
University of Michigan	BB/CC	Henry Paulson	Kelly Bakulski
University of Pittsburgh	BB/CC	Jennifer Lingler	Julia Kofler, Anthony Fabio
Wake Forest University	BB/CC	James Bateman	Suzanne Craft, Samuel Lockhart
Washington University	BB only	Cyrus Raji	Richard Perrin
Yale University	BB/CC	Christopher Van Dyck	

ACKNOWLEDGMENTS

Barbara B. Bendlin, PhD
Robert Rissman, PhD
Andrea Gilmore-Bykovskyi, PhD, RN
William Buckingham, PhD
Ryan Powell, PhD, MA
Jack Hunt, PhD
Mengang Yu, PhD
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Sterling Johnson, PhD

ADRC participants
Neighborhoods Study Collaborators

Center for
Health Disparities Research
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Robert Golden, MD
Jon Audhya, PhD
Rick Moss, PhD

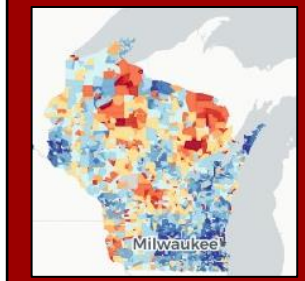
NIA Leadership, Program Officers and Staff

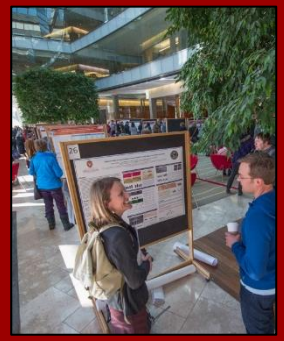
And many, many others . . .

Funding

NIA R01 AG070883 (Kind PI; Bendlin MPI)
NIA supplement 3 R01 AG070883-02 (PIs: Kind/Bendlin)
NIA RF1AG057784 (Kind PI; Bendlin MPI)
NIMHD R01MD010243-01 (Kind PI)
NIA F31AG062116 (PI: Hunt)
NIA P30AG062715 (Asthana PI)
NIA 1P30-AG062429-01 (Brewer PI)
NIA R01 AG077628 (Grill PI; Gillen/Kind MPI)

The NACC database *is funded by NIA/NIH Grant U24 AG072122. Data are contributed by the* NIA-funded ADRCs*: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD).*





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