ONETOX
THE NEURAL EXPOSOME | CHEMICAL THREATS | CHEMICAL SAFETY

NINDS Office of Global Health & Health Disparities

Notice of Funding Opportunity

Role of Environmental Stress in the Health Inequities of Alzheimer's Disease-Related Dementias (ADRD) (R01 - Clinical Trial Not Allowed) (RFA-NS-24-024)

Informational Webinar

August 31, 2023

NIH National Institute of Neurological Disorders and Stroke

Purpose of the Notice of Funding Opportunity (NOFO)

- To identify environmental stressors that impact health inequities in Alzheimer's Disease-Related Dementia (ADRD).
- Determine the mechanistic underpinnings of this stress.
- This NOFO will support mechanistic, translational, and human subject studies to understand the relationship between environmental stressors and health inequities in ADRD.
- It is expected that these studies will identify environmental stressors related to health inequities in ADRD and their clinical relevance.
- Ultimately, these studies should accelerate research towards better therapeutic interventions and quality of life.

Environmental Stress Examples

- heat
- crowding
- air quality
- noise
- poverty
- crime
- violence
- economic disadvantage
- social stress

Key expectations and definitions

- **Studies** on any environmental stressor(s) and any ADRD health inequities that are **supported by the rigor of prior research based on peer-reviewed publications and/or original studies. Strong Premise**.
- "Environmental stress" is stress in a person's surroundings or environment that can cause **strain on human health**, including social stress.
- Supports research on populations in environments that experience **health inequity** driven by geographical location and structural determinants of health (e.g., governance, policies, housing, work, school).
- Applicants are encouraged to use **existing cohorts and databases** when relevant data is available.
- **Multi-exposure** (more than one **environmental stressor**) approaches are **welcomed but not required**.
- Supports studies with **animal and other models** on the mechanisms, pathways, and molecular targets involved in the **causes of ADRD associated with environmental stress**.
- Applicants are strongly encouraged to build integrated **multidisciplinary teams**.
  - **ADRD – Environmental Stress – Heath inequities**

Research Topic Examples – slide 1

- Mechanistic and observational studies with **ADRD patients and controls** to determine the environmental stressors associated with ADRD health inequities.
- Studies that **validate environmental stressors and reveal how they impact health and health equity in ADRD**.
- Effects of environmental stressors on **genetic and epigenetic causes** of ADRD health inequities.
- The relationship between specific stressors and different **ADRD phenotypes**. (within or among the ADRDs)

Research Topic Examples – slide 2

- *In vivo* studies in animals that **mimic known environmental stressors that impact ADRD** health inequities (e.g., environmental enrichment or prolonged isolation studies).
- Transcriptomic, metabolomic, proteomic comparisons between ADRD and healthy age-matched controls living in areas where **environmental stress is more prevalent**.
- Role of **environmental stress related to COVID-19 and ADRD health inequities**.
- Effects of **stress-related segregation on ADRD**. For example, research on how **residential segregation** facilitates the divestment from shared resources that can affect environmental stress, **such as parks, sidewalks, and clean air**.

Expected outcomes

- **Identification of environmental stressors** associated with and that may cause ADRD.
- **Mechanistic** insight that would address the **biological plausibility of these stressors** as both **clinically relevant** and being potential new targets of ADRD.
- Insight into **how environmental stress plays a role** in ADRD-related health inequities.
- Identification of **new therapeutic targets** for treatment of ADRD.
- New **interventional strategies** based on validated stress factors to mitigate health disparity.

Applications that are Responsive

- Basic, translational, and clinical research projects that propose to study the role of environmental stress on the health inequities in Alzheimer's Disease-Related Dementias
  - **Frontotemporal Dementia (FTD)**
  - **Lewy Body Dementia (LBD)**
  - **Vascular Contributions to Cognitive Impairment and Dementia (VCID)**
  - **Mixed-Etiology Dementia (MED), including Clinical Alzheimer's Disease***
    - *Clinical Alzheimer's Disease is Alzheimer's Disease diagnosed on the basis of clinical symptoms alone.
- Impact of environmental stress upon adults
- Environmental stress across all levels of influence including personal, community, and societal interactions
- Research based on clinical data, human samples, and human subjects (**NOT NIH-defined clinical trials**)

Applications not Responsive to this NOFO

- Studies **not** focused on ADRD and environmental stress, as defined herein.
- Studies that **do not** include research on the relationship between environmental stressors and health inequities in ADRD.
- Studies including NIH-defined **clinical trials**.
- Studies only on endogenous stress resulting from pre-existing illness.
  - For example pre-existing illness with a **genetic origin**
- Studies on adverse childhood experiences.
  - Traumatic events that occur in childhood (**0-17 years**) (CDC)

Clinical Trials are not Responsive to this NOFO

- NIH defined clinical trials are research studies in which **one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes**

- If you plan to use human subjects, please review this webpage to make sure your study is not considered a clinical trial https://grants.nih.gov/ct-decision/index.htm.

- NIH Clinical trials https://grants.nih.gov/policy/clinical-trials/definition.htm

There are some important considerations to address when preparing your application

NIH-specific

- **Enhancing Reproducibility through Rigor and Transparency** (NOT-OD-15-103),
- **Implementing Rigor and Transparency** (NOT-OD-16-011), (NOT-OD-18-228)

  - Rigorous experimental design,
  - consideration of sex and other relevant biological variables,
  - authentication of key biological and/or chemical resources,
  - the rigor of the prior research

- **Do not use the Vertebrate Animals section for experimental details**

Further application considerations

- Scientific feasibility
  - preliminary data and the literature should support the hypotheses and proposed studies
- Present sufficient details to evaluate the approach
- Ensure the work meets the goals of the project
- If needed, be sure to address interdependence of aims
- Discuss alternative approaches to research strategies presented
- Describe how the team will communicate

Comparative Toxicogenomics Database
https://ctdbase.org/

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Discover.

1. What human diseases are associated with a gene/protein? (Example)
2. What human diseases are associated with a chemical? (Example)
3. What genes/proteins interact with a chemical? (Example)
4. What chemicals interact with a gene/protein? (Example)
5. What references report a chemical–gene/protein interaction? (Example)
6. What cellular functions (GO terms) are affected by a chemical? (Example)

News

- *July 31, 2023*

52,848,834 TOXICOGENOMIC RELATIONSHIPS!

Keyword Search

All

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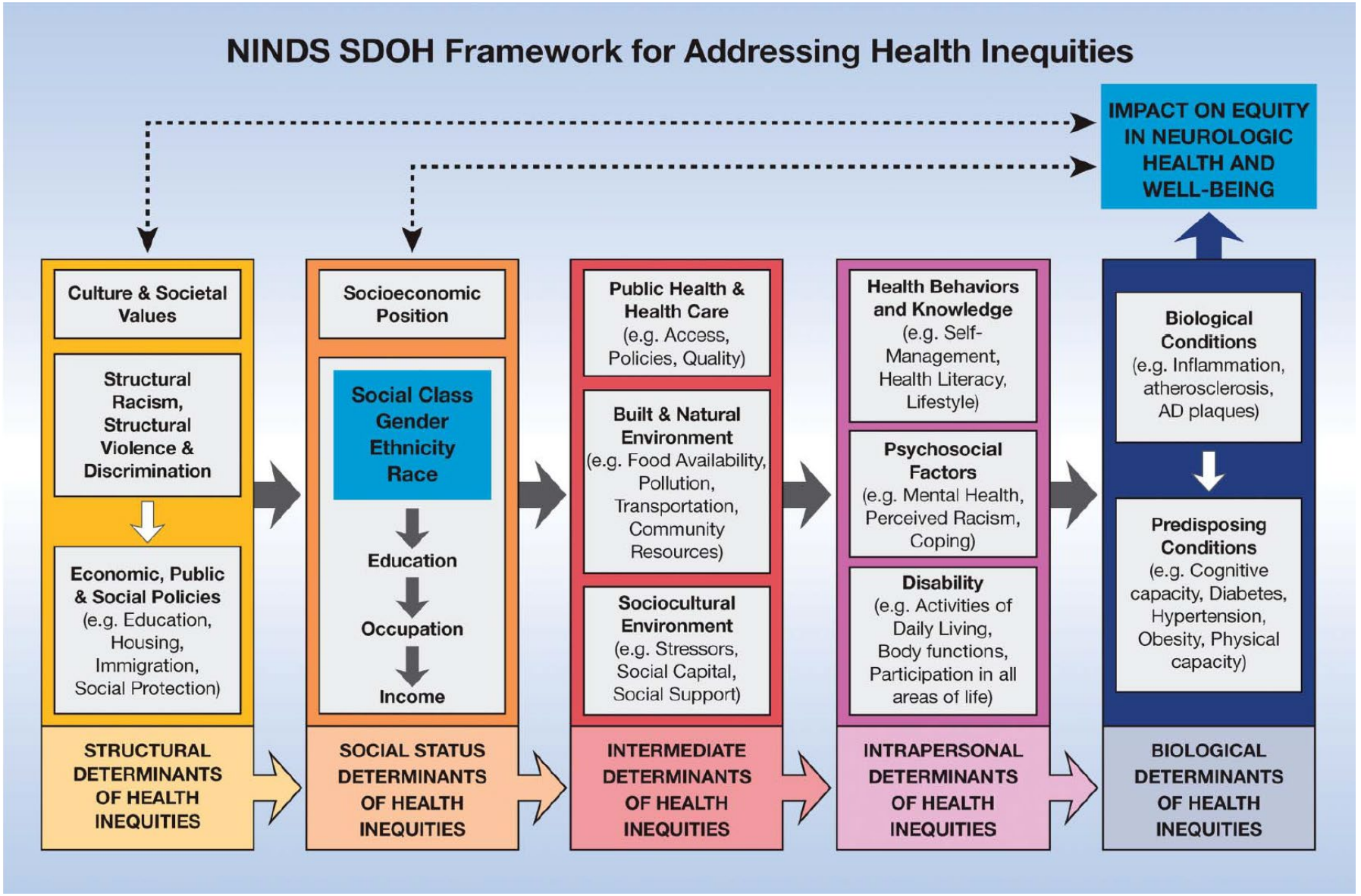
Updated Chemicals

2,5,2',5'-tetrachlorobiphenyl Acetaminophen Acrylamide Amiodarone arsenite Benzo(a)pyrene bisphenol A Cadmium Cadmium Chloride Curcumin diallyl disulfide Dietary Fats dimethylarsinous acid Doxorubicin Estradiol glyphosate Lipopolysaccharides monomethylarsonous acid Norethindrone Acetate Particulate Matter Raloxifene Hydrochloride sodium arsenite T-2 Toxin Tetrachlorodibenzodioxin tobacco tar

NIH National Institute of Neurological Disorders and Stroke

NINDS SDOH Framework



NINDS SDOH Framework

The goal of the NINDS SDOH Framework is to contextualize the biological and intrapersonal determinants of neurological disease, health, and well-being in relation to upstream factors (i.e. intermediate, social status, and structural factors) that have been understudied as points of intervention in neurologic and stroke research.

The relationships among the determinants and pathways linking them to one another are more complex than what the linear model suggests. Yet, the categories of determinants are presented linearly to illustrate the primary ways these factors relate to one another. Each of these topics within the framework reflects potential places to intervene, and the model highlights how factors to the left of that topic shape and have implications for ones to their right.

The framework helps to enhance underlying theory, improve study design, and refine implementation design by highlighting the different levels and scale of causation by refining efforts to contextualize the interpretation of research findings.

NINDS SDOH Framework

- **Structural Determinants of Health Inequities**: The root social, cultural, and political factors that underlie racial, ethnic, and social class patterns in society, health, and well-being.
- **Social Status Determinants of Health Inequities**: The demographic and socioeconomic factors that have acquired social meaning because they are proxies for the Structural Determinants of Health Inequities in ways that have implications for intermediate, intrapersonal, and biological determinants of health.
- **Intermediate Determinants of Health Inequities:** Social, natural, built, economic, health, and political environmental factors that influence exposures, vulnerability, and the consequences of individual and population neurologic health, illness, and well-being.
- **Intrapersonal Determinants of Health Inequities:** Health behaviors (e.g., physical activity, smoking, diet, body mass index), health knowledge, psychosocial factors (e.g., perceived racism), and disability that are influenced by intermediate determinants and in turn influence biological determinants.
- **Biological Determinants:** The direct and indirect bodily systems and processes that embody the accumulation of experience over the lifecourse, resulting in health conditions (e.g., hypertension, diabetes, obesity) that predispose individuals and populations to neurologic disease, illness, and ill-being. **Note: Studies only on endogenous stress resulting from pre-existing illness, for example pre-existing illness with a genetic origin are NOT responsive to this NOFO.**

Key Dates

Mechanism: R01

Budget: Direct costs may not exceed **$500,000/ project period**

Project Period: May not exceed **5 years**, no renewals

ONETOX Contacts

Applicants are encouraged to contact the Scientific/Research Contact listed on this NOFO, especially if human subject studies are planned.

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Richard T. Benson, MD PhD (For health inequities questions)
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Neel Dhruv, PhD (questions related to the NOFO)
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https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/ONETOX-Neural-Exposome