REQUEST FOR APPLICATIONS 24-2

RFA 24-2: INSIGHTS INTO THE HEALTH EFFECTS OF EXPOSURE TO LOW CONCENTRATIONS OF PARTICULATE MATTER

INTRODUCTION

The adverse health effects of particulate matter (PM) are well established by decades of research. Fine PM ($PM_{2.5}$) is a major contributor to morbidity and mortality worldwide (Global Burden of Disease [GBD] 2024; HEI 2024), has been classified as a human carcinogen (International Agency for Research and Cancer [IARC] 2016), and was determined by the United States Environmental Protection Agency (EPA) to have a causal relationship with cardiovascular effects and premature mortality for both short- and long-term exposures (EPA 2019, 2022). To protect public health, governments and organizations across the globe have implemented guidelines and regulations to reduce PM emissions and human exposure. Those efforts have contributed to large reductions in ambient PM concentrations in high-income countries since the 1970s. However, researchers continue to observe adverse health effects of long-term exposure to low $PM_{2.5}$ concentrations in large-scale epidemiological studies, with some studies reporting stronger associations with adverse health outcomes per unit increase in $PM_{2.5}$ at the lowest observed concentrations (Brauer et al. 2022; Brunekreef et al. 2021; Chen and Hoek 2020; Chen et al. 2023; Dominici et al. 2022). In response, the World Health Organization revised its $PM_{2.5}$ annual mean air quality guidelines to 5 $\mu g/m^3$ in 2021 (WHO 2021). In 2024, the EPA lowered the $PM_{2.5}$ National Ambient Air Quality Standard (NAAQS) to 9 $\mu g/m^3$, which is not to be exceeded by the 3-year average of the highest monitor in an area (EPA 2024).

Although there is strong epidemiological evidence of adverse health effects at low concentrations of $PM_{2.5}$ and epidemiological studies suggest that $PM_{2.5}$ is a non-threshold pollutant, many questions remain. First, heterogeneous effect estimates and exposure–response functions have been observed within and between cohorts that could not be explained fully by the available individual- and community-level health and demographic characteristics (Boogaard et al. 2024). Second, it is unclear how individual or repeated short-term high-intensity air pollution exposures might contribute to chronic health outcomes and possibly lead to the observed heterogeneity in the setting of low long-term average $PM_{2.5}$ exposures. Third, although several mechanisms have been reported that support the biological plausibility for health outcomes for which a causal relationship has been concluded, many of the pathways have not been established. Furthermore, toxicology research—one approach to investigate the mechanisms—has historically focused on exposures that are often 1 to 2 orders of magnitude above typical daily air pollution concentrations in many high-income countries today. Thus, there is a need to elucidate the biological pathways specifically linking $PM_{2.5}$ exposures at ambient concentrations observed in high income countries, including concentrations below current health-based standards, with disease and mortality. This RFA solicits applications to address these limitations and to help inform future public health policy.

The Health Effects Institute (HEI) is seeking to fund studies to enhance our understanding of the adverse health effects of exposures to PM air pollution, including long-term exposures to persistent concentrations near or below current health-based standards, as well as single or repeated short-term exposures to high concentrations. Toxicological, clinical, epidemiological, or a combination of such studies should propose novel or improved methods and approaches to address one or more RFA objectives. Research in this area was identified as a priority in HEI's Strategic Plan 2020–2025, and the specific objectives detailed below were identified at HEI's Workshop on the State of the Science of PM Health Effects in December 2024.

STUDY DURATION AND BUDGET GUIDELINES

A total of $2.5 million will be available for this RFA. HEI expects to fund a small number of studies of 2 to 3 years in duration. Preparation of a final report should be included in the budget and timeline for the final year of the study.

BACKGROUND AND RATIONALE

HEI's Contributions to PM Research

HEI previously supported the National Particle Component Toxicity (NPACT) Initiative, which involved coordinated epidemiological and toxicological studies to evaluate the relative toxicity of various chemical and physical properties of PM. The results of those studies indicated that PM composition influences health effects but that there was no simple solution to guide regulatory efforts pointing to specific sources as being more or less toxic than other sources (Lippman et al. 2013; Vedal et al. 2013). More recently, HEI's Low-Exposure Epidemiology Initiative (Boogaard et al. 2024) funded three large epidemiological studies to evaluate long-term PM exposure and mortality in Canada, the United States, and Europe (Brauer et al. 2022; Brunekreef et al. 2021; Dominici et al. 2022). All three studies documented positive associations between mortality and exposure to $PM_{2.5}$ below the level of the annual US NAAQS (i.e., 12 $\mu g/m^3$ at the time of the studies) and current and proposed European Union limit values. Furthermore, the studies observed non-threshold linear (United States) or supra-linear (Canada and Europe) exposure–response functions for $PM_{2.5}$ and mortality. Heterogeneity was found in both the magnitude of effects and shape of the association within and across studies (Boogaard et al. 2024). The variability in the magnitude and shape of the association across the Canadian, United States, and European studies was reduced only slightly in a harmonized analysis that used the same exposure model, outcome definition, population age range, covariates, and statistical models (Chen et al. 2023).

In 2023, HEI hosted a scoping workshop on the State of the Science of PM Health Effects with leading global experts from academia, government, industry, and the nonprofit sector to identify research needs and priorities, with an emphasis on informing United States policy. The areas identified for further research in consultation with the HEI Research Committee and HEI Sponsors included 1) biological plausibility of health effects from low exposure, 2) the role of the indoor environment in evaluating the health effects of outdoor air pollution, 3) health effects of extreme air pollution events, and 4) particles from specific sources (including non-tailpipe motor vehicle emissions, bioaerosols, wildfire smoke, and windblown dust). From workshop discussions, small group brainstorming, and individual voting, the attendees identified and ranked numerous research needs.

Research Priorities Motivating RFA 24-2

Driven by remaining questions from NPACT and the Low-Exposure Epidemiology Initiative, the HEI Research Committee used the workshop findings to develop the objectives for this RFA. The primary motivation is to better understand the epidemiological evidence for health effects associated with exposure to such low concentrations of ambient $PM_{2.5}$. Several hypotheses were identified that might independently or collectively contribute to the associations and reported heterogeneity in the epidemiological findings, including (in no specific order) exposure to specific microenvironments, the role of individual or repeated high-intensity short-term PM exposure in contributing to the development of disease, or increased susceptibility or vulnerability in subgroups of the population. These hypotheses that might help to explain heterogeneity are discussed further in the following sections. Studies that can help distinguish between these

potential sources of heterogeneity or could help to inform the biological plausibility of PM health effects at low-dose exposures would be useful to support future policy.

Exposure Microenvironments

Despite the development of extensive monitoring networks and sophisticated, highly spatially resolved exposure assessment methods, there remain complex air pollution microenvironments (i.e., time-, location-, and pollutant-specific environments) that can be difficult to capture in large-scale population studies. Low annual average ambient $PM_{2.5}$ concentrations determined for a specific area (e.g., metropolitan statistical area) do not preclude higher exposures to ambient $PM_{2.5}$ or other confounding ambient pollutants in specific locations, including near major roadways, airports, railyards, or other important sources. Previous studies have controlled for many common co-pollutants, including ozone and nitrogen dioxide, but these co-pollutants can exhibit higher local variability than captured with existing exposure assessment methods with spatial resolutions of 100 m to 1 km. Other co-pollutants, including air toxics and ultrafine particles, are relatively understudied, although they might exhibit lower spatial correlations with $PM_{2.5}$.

Finally, although annual average $PM_{2.5}$ concentrations have decreased in the United States, the particle size, composition, physical and biological characteristics can vary widely over space and time. In particular, certain source-specific PM emissions could potentially elicit higher toxicity per unit mass, can be specific to a microenvironment, and can change over time. These changes might be influenced by complex factors such as climate change or the energy transition that lead to increases in wildfire smoke or non-tailpipe emissions, respectively, in some areas.

High-intensity air pollution events

Low annual average $PM_{2.5}$ concentrations do not preclude exposure of large segments of the population to very high $PM_{2.5}$ exposure on a limited number of days. Studies that examine the health effects attributed to long-term exposure to ambient air pollution typically assign exposure by averaging concentrations over one or more years. However, exposures fluctuate on a daily, weekly, or monthly basis. High-intensity air pollution events, in isolation or repeated over time, such as those caused by wildfires or dust storms, can expose people to different source-specific PM mixtures, might have different relative toxicity, and have the potential to influence long-term health and disease development in ways that have not been adequately captured over smoothed annual exposure assessments. These air pollution events can occur under different and potentially meaningful temporal patterns or could elicit a cumulative effect over time. At the same time, high-intensity air pollution events often occur in places with sparse ground monitoring of air quality and at times when satellite remote sensing observations are obscured by clouds. In the United States, these events can also be excluded for regulatory purposes despite increasing in frequency in some regions.

Biological plausibility

Linking toxicological, clinical, and epidemiological studies with complementary endpoints or otherwise triangulating evidence is needed to inform biological mechanisms at ambient concentrations, including concentrations below current health-based standards. Mechanisms that lead to systemic health effects and morbidity outcomes, particularly metabolic, cardiovascular, and neurological diseases, relevant to the evolving population demographics in the United States (such as aging populations), would be useful. Documenting early clinical or subclinical markers of effect that have the potential for early intervention, as well as documenting age-dependent disease onset and progression, could potentially prevent or mitigate downstream health outcomes.

Susceptibility and Vulnerability

Identifying at-risk populations involves consideration of both susceptibility and vulnerability[1]. Certain populations and individuals at different life stages—such as children and older adults, individuals with pre-existing disease, communities of color, and low-socioeconomic-status communities—might be considered at higher risk for $PM_{2.5}$-related health effects. Marginalized groups are more likely to live in areas with higher air pollution exposure and lower health-promoting resources, resulting in exposure and health effect disparities. Furthermore, individual or community-level factors, or both, might increase or decrease risk to PM exposure and contribute to the heterogeneity in the observed PM health effects. Those factors can help to inform the biological mechanisms of the health effects observed at ambient concentrations, including concentrations below current health-based standards. To inform effective health policy, there is a need to identify factors that contribute to gradations of vulnerability and could be modified at the individual or community level to decrease susceptibility and vulnerability.

OVERALL OBJECTIVE

HEI is seeking to fund studies to provide further insights into the health effects associated with long-term exposures to persistent ambient PM concentrations near or below current health-based standards. Such studies could meaningfully influence the interpretation of the overall body of the epidemiological research by proposing novel or improved methods or approaches, linking multiple sources of evidence to identify important sources of heterogeneity in the health effect estimates or exposure–response functions, or further informing biological mechanisms and disease processes.

SPECIFIC OBJECTIVES

In the context of the overall objective, HEI seeks to fund studies that can accomplish at least one of the following specific objectives:

1. Evaluate the influence of individual or repeated short-term high-intensity air pollution exposure events on long-term health and disease development.
2. Develop, validate, and apply novel or improved exposure assessment methods suitable for estimating exposures to specific microenvironments, PM size fractions, PM from specific sources, or important or understudied co-pollutants. Assessment of individual PM components without linkage to specific source emissions will be considered nonresponsive.
3. Identify markers of disease onset or progression or modifiable factors that confer increased susceptibility or vulnerability to the health effects of PM.
4. Provide evidence of the biological mechanisms or disease processes of the health effects of PM.

[1]Susceptibility and vulnerability is defined in various ways in the scientific literature. Here, we define susceptibility as innate (e.g., genetic) or acquired (e.g., smoking status) sensitivity that increases the risk of health effects occurring with exposure. We define vulnerability as an increased risk of exposure related health effects due to factors such as those related to socioeconomic status, reduced access to health care, or other exposures.

CRITICAL STUDY DESIGN CONSIDERATIONS

Study Designs

The RFA is open to toxicological, clinical, and epidemiological studies, or combinations of these (no specific order of priority). Toxicological proposals must clearly articulate the relevance of the research to the human health effects of PM at low ambient concentrations.

Geographic location

Proposed studies must clearly articulate the relevance of the research to the human health effects of PM in the United States.

Exposure

Studies must address long-term $PM_{2.5}$ exposure at concentrations relevant to current ambient pollution in the United States; this includes studies that are investigating high-intensity air pollution exposure events. For this RFA, long-term exposure on the human scale is defined as a duration of months to years, following the definition used in the World Health Organization Air Quality Guidelines (WHO 2021). In epidemiological studies, the description of the exposure assessment should include the main data sources or models, the spatial and temporal resolution (including alignment with the health data), and any exposure calibration or validation.

Health outcomes

Applications should provide a clear rationale regarding the choice of health outcomes in relation to earlier research and the research questions being addressed. Measurement and validation of the health outcomes must be clearly described.

Precision and statistical power

Applications should document and discuss the expected precision and statistical power of their estimates. Assumptions needed for such calculations should be guided by relevant published literature.

Statistical methods

Applications should propose appropriate statistical and analytical methods and propose sensitivity analyses where appropriate. Epidemiological studies that apply novel multi-state modeling (i.e., a model of the transition between stages of health and disease such as initiation, progression, regression, and relapse [Le-Rademacher et al., 2022]) or novel methods to control residual confounding or otherwise advance causal inference are encouraged.

Budget

Budgets should closely align with the selected specific objective(s) and scope of work. Preparation of the final report should be included in the budget.

RESEARCH TEAM

The research team should possess the full range of expertise necessary to conduct the proposed research. The Principal Investigator (PI) must demonstrate a record of producing high-quality and objective research in areas relevant to the proposed work and be affiliated with an established research organization.

HEI strongly encourages applicants to diversify their research teams by including individuals from groups that are underrepresented in the relevant disciplines as outlined in the National Institutes of Health definition of underrepresented populations in the US Biomedical, Clinical, Behavioral and Social Sciences Research Enterprise[2]. Furthermore, to the extent appropriate for the study location(s), applicants should be attuned to and knowledgeable about the communities in which the studies will take place. The team's technical proposal ideally will be informed by engagement with experts who represent multiple sectors (e.g., academia, communities, regulatory and public health agencies, industry, and non-governmental organizations) and will include them in research, as appropriate.

The proposal must clearly identify each team member, their affiliation, and role in the research. The team should have access to study sites (as evidenced by letters of support in the proposal, if applicable) and have or obtain access to facilities, equipment, and instrumentation needed to support the proposed research. If investigators plan to use data or materials (e.g., filter samples) from previous research, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. The application should include a letter from the investigator who owns any data or the materials that states willingness to share the data with the applicant and with HEI, if requested.

POLICY ON DATA ACCESS

Providing other researchers with access to data is an important element in ensuring scientific credibility and is particularly valuable when studies are of regulatory interest. HEI has a long-standing policy to provide access to data for studies that it has funded in a manner that facilitates the review and validation of the work. The policy also protects the confidentiality of any subjects who may have participated in the study and respects the intellectual interests of the investigators who conducted the study. Please refer to the HEI Policy on the Provision of Access to Data Underlying HEI-Funded Studies.

Applicants will be expected to include a plan for data sharing and accessibility at the end of the study. Where data are provided by a third party, a process for other investigators to obtain and work with the data should be outlined.

[2] The National Institutes of Health definition of underrepresented populations includes individuals from racial and ethnic groups underrepresented in health-related sciences on a national basis, individuals with disabilities who are defined as those with a physical or mental impairment that substantially limits one or more major life activities, and individuals from disadvantaged backgrounds, recognizing that women from these three backgrounds face particular challenges at the graduate level and beyond in scientific fields (Source).

APPLICATION PROCESS AND DEADLINES

The submission and review of applications for RFA 24-2 will entail a two-stage process.

- Applicants should submit a **Preliminary Application by November 4, 2024**. The HEI Research Committee will discuss the preliminary applications and invite a limited number of investigators to submit a full application. Responses will be provided in January 2025.
- Invited applicants should submit a **Full Application by February 17, 2025**. Full applications will be reviewed by external reviewers and an ad-hoc Special Review Panel before consideration by the Research Committee. Applicants will be notified about the funding decision by June 2025.

PRELIMINARY APPLICATION

Applicants should submit a Preliminary Application using the form provided on the HEI website. The preliminary application should include the following information: title, abstract, scientific rationale, a brief description of the study aims, design and methods, and anticipated results. It should also briefly discuss the applicant's qualifications and include a biographical sketch for each co-investigator (maximum two pages per person). An estimated total budget and study duration should be provided. No detailed budget forms are needed at this stage.

The preliminary application should not exceed **4 pages** (excluding references and biosketches). Please note that the required font size is 11 point with 1-inch margins.

Submission and Deadline

Preliminary applications should be submitted electronically to funding@healtheffects.org no later than **November 4, 2024**. HEI will acknowledge receipt of the application. Questions regarding the RFA and how to apply should be directed to Dr. Eva Tanner (etanner@healtheffects.org).

FULL APPLICATION

Invited full applications should provide in detail the study aims, design, rationale, methods, and statistical analyses. If data from other studies are going to be used, information on the type of data available (including the period, location, and frequency of when the measurements were taken) and quality assurance should be included. Investigators should also discuss whether they will need to obtain IRB approval. Where applicable, a letter from the investigator who owns the data should be submitted and state their willingness to share the data with the applicant and with HEI, if requested (see HEI Policy on the Provision of Access to Data Underlying HEI-Funded Studies). In addition, the full application should include a plan for data sharing and accessibility at the end of the study.

Investigators invited to submit a full application should use forms F-1 to F-12 and consult the Instructions for Completing the Application. Application forms can be downloaded from https://www.healtheffects.org/research/funding. Please note that the required font size is 11 points with 1-inch margins.

Form F-12 is separated from the rest of the application upon receipt. The data are kept confidential and not considered for funding decisions; HEI strongly appreciates completion of this form to track diversity of applications and funded investigators in an effort to continue to invest in and expand HEI's investment into

diversity, equity, and inclusion efforts as part of its 2020 commitment. **The application forms should be turned into a PDF with appropriate bookmarks before submitting.**

Submission and Deadline

Invited Full Applications should be submitted to **funding@healtheffects.org** no later than **February 17, 2025**. The application should be in PDF format with a maximum file size of 20 MB. HEI will acknowledge receipt of the application.

Full applications without pre-submission of a preliminary application and invitation from the Research Committee will not be considered.

EVALUATION PROCESS FOR FULL APPLICATIONS

Full applications will be evaluated in a two-stage process: an external review followed by an internal review.

EXTERNAL REVIEW

Applications undergo a competitive evaluation of their scientific merit by an ad hoc panel of scientists selected for their expertise in relevant areas. Applications might also be sent to external scientists for additional evaluation, if necessary, in areas of expertise that are not covered by the Panel or where there are conflicts of interest. The panel will evaluate applications according to the following criteria:

- Relevance of the proposed research to HEI's goals
- Scientific merit of the proposed study design, approaches, methodology, analytic methods, and statistical procedures
- Personnel and facilities, including
    - Experience and competence of the PI, scientific staff, and collaborating investigators
    - Extent of collaboration among investigators in pertinent fields who will contribute to the conduct of the study
    - Adequacy of effort on the project by scientific and technical staff
    - Adequacy and validity of existing data and data to be collected
    - Adequacy of facilities
- Reasonableness of the proposed cost

INTERNAL REVIEW

The internal review is conducted by the HEI Research Committee and generally focuses on the applications ranked highly by the external review panel. The review is intended to ensure that the studies recommended for funding constitute a coherent program and address the objectives of the Institute. The Research Committee makes recommendations regarding funding of studies to the Institute's Board of Directors, which makes the final decision.

CONFLICTS OF INTEREST

HEI's procedures for conflicts of interest are similar to the guidelines set forth by NIH. Members of HEI's sponsor community are excluded from participating in RFA development, applying for support, application review, and funding decisions.

HEI invites external reviewers (or in the case of a major RFA, Review Panel members) who are unlikely to have a conflict of interest with the proposal(s) they are asked to review. A conflict occurs when the reviewer

is named on the application in a major professional role; the reviewer (or close family member) would receive a direct financial benefit if the application is funded; the PI or others on the application with a major role are from the reviewer's institution or institutional component (e.g., department); during the past three years, the reviewer has been a collaborator or has had other professional relationships (e.g., served as a mentor) with any person on the application who has a major role; the application includes a letter of support or reference letter from the reviewer; or the reviewer is identified as having an advisory role for the project under review. In addition, HEI Staff screen external reviewers for potential conflicts of interest with other applicants who have submitted a proposal under the same RFA. All Panel members also complete a confidential conflict of interest form and are asked to recuse if there is any actual or perceived conflict of interest.

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