American Heart Association.

Migraine as a Risk Factor for Stroke And Cardiovascular Disease

Contents

Key Dates

RFA Posted:	December, 2022
Letter of Intent Pre-proposal (Required via email) Deadline:	January 23, 2023
American Heart Association Pre-proposal invitations:	January 31, 2023
Application Deadline (for invited participants only):	March 6, 2023
American Heart Association Peer Review:	March, 2023
Notification of Awards:	May, 2023
Award Start Date:	July 1, 2023

Overview

Migraine, particularly migraine with aura, is a risk factor for stroke.[1,2] There is growing evidence, moreover, that migraine with aura may also be a risk factor for other cardiovascular diseases, including myocardial infarction.[1,2] The mechanisms for these associations remain uncertain. Potential explanations include comorbid risk factors such as smoking, medications used to treat migraine, changes in physical activity and diet, a pro-inflammatory state and thrombophilia, vasospasm, and structural cardiac disorders such as patent foramen ovale.[1,2] Migraine is significantly more common in women than men, with approximately 25% of women experiencing migraine at some point in their lives.[1,2] Migraine also changes throughout the lifecourse, with boys and girls sharing the same prevalence of migraine before puberty, but with the prevalence in women increasing dramatically after menarche.[2] Episodes of migraine also change frequency during pregnancy and at menopause. These findings suggest that hormonal factors are also likely to play a role in causing migraine or affecting its symptomatic expression.

Longitudinal population studies and electronic health record data in the United States and globally have provided the bulk of evidence to date for our understanding of migraine and its association with stroke and cardiac disease. Many questions remain unanswered however, including (1) the mechanistic relationship between migraine and cardiovascular disease; (2) the relative importance of migraine with aura versus migraine without aura; (3) potential ameliorating effects of medications like statins; (4) the effects of social determinants of health and disparities on migraine prevalence and expression; (5) sub-phenotyping of migraines and risk of cardiovascular disease; (6) imaging data and migraines; (7) identifying predictors of higher risk of CVD in patients with migraine and many others.

The purpose of this Request for Proposal (RFP) announcement is to use large currently available databases (studies or electronic health record data) with information on migraine and cardiovascular disease, in combination with data science approaches, to assess migraine as a risk factor for cardiac disease and stroke.

This RFP promotes data harmonization and analysis of key longitudinal population studies or electronic health record data on which our current understanding of migraine and cardiovascular disease is based, including but not limited to the American Migraine Study I and II, American Migraine Prevalence and Prevention Studies, National Health Interview Survey, Nurses' Health Study, and the Women's Health Initiative. These data may also be combined with new data including but not limited to the UK Biobank and other datasets. Projects with data on social and structural determinants of health in migraine, genetic data, and behavioral data will all be considered. Projects that seek to explore fairness and equity in risk models will also be considered.

Research supported by this RFP include analysis of epidemiological studies, clinical trial data, electronic health record data, imaging data, genetic data, proteomic and /or metabolomic data or other already accumulated datasets. This RFP does not support establishment of new cohorts or collection of new data on existing cohorts.

[1] Adelberg et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ, 2018;360:k96.
[2] Oie et al. Migraine and risk of stroke. J Neurol Neurosurg Psychiatry. 2020;91:593-604.

Who **we're looking for**

Our goal is to create a collaborative group of experts in migraine, cardiovascular disease and stroke, biostatistics and data science to study the cardiovascular comorbidities, correlates, and complications of migraine. This group will explore unanswered questions about migraine using new ideas from across different fields and new data.

Before you apply

- For teams that are invited to submit a full application, the project lead must be an American Heart Association professional member.
    - Join or renew when preparing an application in Proposal Central, online or by phone at 301-223- 2307 or 800-787-8984.
    - Membership/Partnership processing takes 3 to 5 days; do not wait until the application deadline to renew or join.

- Projects can include collaborators from multiple areas of expertise; however, the project proposal must be submitted by a project lead representing an academic or non-profit organization based in the United States.

- Any member of the team can serve as the project lead. Projects may have co-investigators from other collaborating organizations. We strongly recommend that organizations identify only one project lead per project.

- Preference will be given to applicant organizations that are institutes of higher education, public entities, or nonprofits that are tax exempt under Section 501(c)(3) of the Internal Revenue Code and are not private foundations or Type III supporting organizations. Other types of nonprofit and for-profit organizations are also eligible to apply. The American Heart Association may require additional documentation.

- Awardees will be selected based on health impact and scientific merit.
- Projects will be considered that:
    - Are aligned with the American Heart Association's mission and goals
    - Provide a clear plan for bringing together datasets and experts across fields to take a fresh look at migraine.

- Organizations that are currently funded through other American Heart Association funding mechanisms can apply.

- Organizations can submit multiple proposals.

- Applicants *will be required* to leverage the established cloud-based infrastructure of the American Heart Association's Precision Medicine Platform to measure, harmonize, and standardize migraine data from across different cohorts.

- Applicants will be required to participate in distributed peer review for this award.

How to apply: pre-proposal

1. Pre-proposal Letters of Intent are **mandatory** and are **due Jan 23, 2023, at 5 pm CT**. Email your Letter of Intent in a PDF Format to datascience@heart.org
2. All Letters of Intent will be reviewed. Those responsive to the RFP will be invited to submit a full application.
3. Your letter of intent (2 page limit) should include the following information about the proposed project:
   - Project title
   - Name and contact of project lead
   - Names, titles, affiliations, relevant expertise of co-investigators
   - Names of any collaborating organizations
   - Data to be used
   - Approximate budget per year of the study
   - Planned approach and activities to achieve the goals

How to apply: invited proposal

Applications must be submitted using ProposalCENTRAL, the American Heart Association's online submission portal. Deadline is **March 6, 2023 at 5 pm CT**.

Only invited Applicants may submit a full proposal. Applications invited to submit a proposal are chosen from the Letters of Intent. See *Details and requirements* for additional guidance.

A plan of action to use the research to establish a common language and standard set of metrics for measuring the impact of various social determinants of health on quality-of-life related risks and outcomes.

A research plan that can be up to 6 pages (12-point font, single space, 1-inch margins on all sides):

1. Operational plan with links to the data analysis plan (see below)
2. Rationale
3. Expertise (names, titles, affiliations, relevant expertise)
4. Methods/results section:
    - A clear description of the tools and types of analysis grantees will perform in the workspace on the Precision Medicine Platform
    - An explanation of how the Precision Medicine Platform will be leveraged to share data and code within the team and to accelerate collaboration across research communities
    - A plan for interoperability of data with national or international standards
5. Expected outcomes and deliverables, a timeline, and project success milestones
6. A data analysis plan that includes a link to the Jupyter notebook created in a workspace on the Precision Medicine Platform. The submitted notebook should be in HTML format. In Jupyter, follow these steps:
    a. In the File Menu, selecting *Download as > HTML (.html)*. The HTML file will download to a temporary downloads folder.
    b. Re-upload the HTML file to the workspace by clicking the *upload* icon in JupyterLab or clicking the *Upload* button on the Jupyter Home tab.
    c. In the workspace, save the notebook in the /mnt/workspace/Export_Files directory which will sync the notebook with the workspace portal.
    d. The notebook will be listed within the Export files section on the workspace portal page. To the right of the notebook, click the box with the arrow that shows "Share for Grant Application" when you hover over it.
    e. Sharing the notebook creates a static link that will be used by the peer review team.
7. Discussion of how the proposal is aligned with and will leverage:
    - The American Heart Association's mission and goals (required)
    - The American Heart Association's Precision Medicine Platform (required)
8. Works Cited (pages for Works Cited are not included in 6-page limitation)
9. NIH biosketches of all key personnel (not included in 6-page limitation)
10. Project technical summary to briefly describe the proposed work (not included in 6-page limitation)
11. Non-scientist summary to describe your work to people without science or medical backgrounds. Address the following: (not included in 6-page limitation)
    - Problem being addressed
    - Specific questions and how you will attempt to answer them
    - Potential impact of this work
12. Budget information including:
    - Salary and fringe benefits of the project lead, collaborating investigators, and other participating research staff or faculty.
    - Project-related expenses, such as salaries of technical personnel essential to the conduct of the project, travel, and publication costs in accordance with institutional and American Heart Association policies. Please note that the American Heart Association does not fund the costs of program implementation or operations beyond what is established in an approved budget.

- Maximum of 10% institutional indirect costs may be claimed on the award.
- *The awardee will be responsible for overseeing the total budget for the grant. If awarded, the project lead and the institution assume an obligation to expend grant funds for the research purposes set forth in the application and in accordance with all regulations and policies governing the grant programs of the American Heart Association.*

Details and requirements

Duration
Up to 2 years from date of funding, contingent upon milestones and timelines being met.

Number of Awards
The American Heart Association anticipates awarding five grants for this RFP.
The American Heart Association reserves the right to determine the final number of awardees.

Award Amount
- $150,000/year ($300,000 cash total) including 10% indirect costs.
- An additional Amazon Web Services (AWS) service credit (up to $50,000/year) for use of the American Heart Association Precision Medicine Platform may be provided for computational time, use of AWS tools and infrastructure, and storage. Credit amount will be determined based on estimated need over duration of the grant.

Precision Medicine Platform, research environment, trial workspace
Projects must be conducted via the American Heart Association's Precision Medicine Platform, powered by Amazon Web Services.

Each team may be eligible to receive Amazon Web Services computational credits to cover the cost of cloud computing for a secure and private workspace on the American Heart Association's Precision Medicine Platform to enable investigators in each team to collaborate and analyze data securely.

Data analysis is enabled in secure workspaces by a web interface that allows researchers to code in various languages, including R and Python, and to use statistical software including but not limited to SAS and R studio. The most up-to-date machine learning and artificial intelligence software available from Amazon Web Services is also included. Researchers are also able to install their own tools.

The American Heart Association asks that the grantees also accelerate collaboration through the sharing of data and code as well as the coordination for interoperability of data to facilitate findability and sustainability. The American Heart Association fully supports the FAIR (**F**indable, **A**ccessible, **I**nteroperable and **R**eusable) guiding principles of data stewardship.

The Platform is HIPAA and FedRAMP compliant. Learn more about the Platform's Security Information.

To learn more about the Precision Medicine Platform:
- Overview
- Full list of available analytical tools
- Videos:
    - Learn more about the platform – video 1
    - Explore the capabilities of the platform – video 2

1. Register here for a 60-day complimentary trial workspace to use during the application period
2. Once registered, login and go to Data - Explore & Request and click Request Workspace (do not select any datasets).

3. Within the form, please include the following text for your Researcher Purpose:
Trial Workspace for Migraine RFP.

Interim and Final progress reports

Awardees must report progress on a minimum annual basis. Progress reports may take the form of a required written report in addition to video conferencing, phone calls, and/or face-to-face visits. Reporting will be focused on achievement of stated milestones as indicated in the project timeline. The American Heart Association reserves the right to request additional updates, site visits, or reporting.

Public access

The American Heart Association's public access policy requires that all journal articles resulting from American Heart Association funding be made freely available in PubMed Central and attributed to a specific American Heart Association award within 12 months of publication. It is the responsibility of the awardee to ensure journal articles are deposited into PubMed Central.

Open Data

Any factual data that is needed for independent verification of research results must be made freely and publicly available in a repository approved by the American Heart Association within 12 months of the end of the funding period (and any no-cost extension). An exception to this is if the data sets were funded by NIH and they are stored on dbGaP.

For more information on the above policies, see the American Heart Association's Open Science Policy webpage.

Peer Review

Peer review for this program will be conducted using a distributed peer review approach (Merrifield and Saari, Astronomy and Geophysics, 50, 4.2, 2009). This is also known as the Mechanism Design Proposal Review Process.

Distributed peer review relies on the principles of a traditional peer review panel: academic integrity, rigor, transparency, and a desire to advance the best science. As opposed to traditional peer review, distributed peer review capitalizes on the expertise of the applicant pool and incentivizes timely review in fairness to all applicants. Additionally, this peer review mechanism exposes applicants to new ideas and could foster new potential collaborations.

All applicants who submit a proposal will be required to serve as a peer reviewer within this program and will be assigned several proposals (could be 6-9 as an estimate) for review. By agreeing to the program terms at the time of proposal submission, the principal investigator is concurrently agreeing to serve as a peer reviewer within this program and meet all peer review expectations and requirements. Principal investigators will declare conflicts of interest and will only be assigned proposals for which they do not have an institutional or individual conflict; PIs (reviewers) are bound by all other requirements associated with peer review. PIs will be provided ~30 days to complete review and scoring of the proposals to which they are assigned.

Only peer reviewers who complete their assigned reviews and record their scores in a timely fashion will in turn have their own proposal evaluated for advancement. Brief comments including bulleted strengths and weaknesses are required. Principal investigators who have not completed their reviews nor submitted their scores by the stated deadline will have their proposals withdrawn and returned as not in compliance with the program announcement, and they will not receive scores should any have been completed for their proposal. Peer review will require submission of scores using ProposalCentral; there will be no peer review panel discussions or meetings. All other AHA Peer Review processes apply.

Additional Requirements

- The projects submitted can have no scientific or budgetary overlap with other work funded by the American Heart Association or any other source.
- Any inventions, intellectual property, and patents resulting from this funding are governed by the American Heart Association's Patent, Intellectual Property and Technology Transfer Policy.
- The applicant/awardee and institution are responsible for compliance with all American Heart Association research award policies and guidelines for the duration of any awards they may receive.
- Visit the Research Programs Awards Policies page for more information on this topic: American Heart Association Policies Governing All Research Awards

For questions and assistance: datascience@heart.org