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Stroke research with longitudinal cohort studies: A beginner's guide

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Transitioning from clinical training to a post-doctoral fellowship or to academia requires publishing research. A first step is accessing the mentorship, data, protected time, and resources to develop research skills and initiate projects. Trainees and early career investigators can undertake research in the basic sciences, use clinical trial data, or perform research with observational studies. This article focuses on how to pursue research with longitudinal cohort studies, an important type of observational study.

As opposed to an experimental study, where investigators manipulate or assign an exposure or intervention, in an observational study participants are defined according to their *observed* exposure status. Potential data sources for such studies include administrative or questionnaire databases, medical records, stroke registries, and population-based epidemiological studies.

Longitudinal cohort study definition

Longitudinal cohort studies follow a designated group of individuals, often from a fixed geographic region, over a period of time to track them for disease outcomes.[1] Participants are selected who are free of the outcome at the beginning of the study, but are at risk for developing the disease. When testing a hypothesis, a group of participants without a specified exposure is the 'referent' or comparison group. Investigators compare disease incidence between the exposed and unexposed individuals over a period of follow-up. The study design facilitates investigating disease risk factors, which are measured or assessed

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prior to the outcome event. Longitudinal cohort studies can describe trends in disease incidence over time, the effect of clinical decisions or treatments on outcomes, and analyze risk factors or biomarkers for prediction of disease. The Table lists examples of cohort studies that investigate stroke.

Advantages for early career investigators

For trainees and early career investigators, there are appealing advantages of research with cohort studies, both with regard to the science as well as to the research environment. Many of these studies have extensive, well-curated, and high-quality datasets from which to test hypotheses. The Framingham Heart Study (FHS)[2, 3], for example, celebrated its 70th year in 2018. Over 15,000 FHS participants have contributed to research studying stroke, dementia, Parkinson's disease, and epilepsy, among other outcomes. The FHS has a rich dataset including assessment of cardiovascular risk factors (determined via interview, questionnaires, clinical evaluation, and review of medical records), blood biomarkers, neuroimaging, cognitive testing, and a brain donation program. Data from longitudinal cohort studies often contain more detail than administrative datasets, such as information on stroke subtype, stroke severity, and disease-specific mortality. Outcomes relevant to cerebrovascular disease may be measured prospectively, such as functional status, cognitive dysfunction, quality of life, and depression. Research with higher quality data can lead to higher impact publications.

When initiating research with a longitudinal cohort study, early career investigators might begin by using previously collected data. It is also possible to propose collection of new data at follow-up assessments ("ancillary studies") or use existing resources to create new datasets. An example of the latter is using previously collected blood samples to measure novel serum biomarkers. The National Institutes of Health (NIH) have funding opportunities that encourage the use and development of existing cohort data. Research funding and fellowship opportunities are also available through medical specialty societies, philanthropic foundations, and non-profit organizations.

Longitudinal cohort studies provide an excellent research training environment. Ongoing studies often have well-established research teams and senior investigators with extensive experience. Study investigators may have diverse research interests and come from varied clinical and scientific backgrounds, including neurology, cardiology, neuropsychology, neuroimaging, neurobiology, epidemiology, biostatistics, genetics, and bioinformatics. A study may have multiple principal investigators of funded grants. Senior members often have the mentoring experience and resources to oversee training for early career investigators and they frequently mentor individuals from outside of their own institution. Access to high quality data, mentorship, and training in the research process are critical for launching a career in clinical research.

Challenges in research using longitudinal cohort studies

Early career investigators may find it daunting to attempt research with extensive datasets from long-running cohort studies. Many important or straightforward research questions (the

"low-hanging fruit") have been studied or published. To propose a feasible research question, the methods for defining exposures and outcomes need to be clearly understood. For example, an exposure such as physical activity level can be measured by self-report questionnaire, daily activity logs, or via a wearable device, such as an accelerometer or smartwatch. Stroke mortality can be determined using death certificates, medical records, or review by an endpoint committee. Often, guidance from experienced senior investigators, biostatisticians, and data managers is necessary to understand and interpret the available data. Working with epidemiologists and experienced biostatisticians is important to understand the nuances of the data and to use appropriate statistical approaches. If you are a collaborator from another institution, you may need to provide funding for the biostatisticians to run the analyses.

There are limitations to performing research with longitudinal cohort studies. Prospective cohort studies can measure disease incidence, but do not adequately estimate prevalence, unless the cohort is representative of the larger population. Rare conditions are difficult to examine because of low numbers of events. Depending on the cohort size, there may even be few events for relatively common conditions. Loss to follow up can be a problem. As with any observational study, there are sources of bias or design aspects that can compromise the validity of findings. Selection bias can occur when participants are differentially chosen to undergo certain research assessments. For example, participants who undergo MRI tend to be healthier than those that do not or cannot (e.g., contraindicated due to a pacemaker). Important variables that are not measured during a study can cause confounding. Misclassification bias can occur depending on how information is collected and interpreted. Ascertainment of stroke events using medical records and review by a neurologist will 'phenotype' a stroke with more rigor than an event determined by history or self-report. Finally, external validity is questioned if the cohort is not representative of the larger population, for example with regard to distribution by sex, race, or ethnicity.

How you can get involved

Before submitting a proposal as a new investigator, become familiar with the cohort study, discuss your interests with study co-investigators, and develop a feasible research idea. The study website may have information about the study, list participating institutions and investigators, and highlight previous publications. Cohort study designs are frequently published in journals. Familiarize yourself with recent publications in your field. Some studies have generated thousands of publications, so developing a new and viable research idea is important.

Obtain a background in clinical epidemiology and biostatistics early during training. Understand study design, sources of bias, and how to interpret measures of association, confidence intervals, and P values. Consider incorporating this education into a postdoctoral fellowship, earning an advanced degree, or taking summer courses. Your institution may offer tuition remission for coursework, or your department may be willing to support you. There are also online courses in introductory clinical epidemiology and biostatistics.

Communicate directly with investigators associated with the study. Identify senior investigators and use tools such as NIH RePORTER (http://projectreporter.nih.gov/reporter.cfm) to learn about their research. Ask to join a lab meeting, teleconference, working group, or email listserv, if possible. Discussing your ideas can help refine your research question. Study investigators can help you assess if your project will have enough statistical power. You may find a similar proposal was made by another investigator, or a similar project was begun but never published. This is an opportunity to seek mentorship. A mentor can sponsor you and help with submitting your research proposal.

Research with longitudinal cohort studies can be performed independently, requesting data from repositories such as the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC)[4] or the National Center for Biotechnology Information's genetic repository database of Genotypes and Phenotypes (dbGaP). However, collaborating with study investigators has distinct advantages. As a new collaborator, you gain access to the investigators' detailed knowledge of the study. Statistical support may be provided for your project. You may need to submit your proposal to an Executive Committee or other review body and determine the correct process for getting Institutional Review Board approval.

Conclusions

Research with longitudinal cohort studies can provide significant opportunities for early career investigators. These studies often have extensive data sets and experienced co-investigators working on high-quality science. Beyond opportunities to publish, joining a research team at a cohort study can open doors for mentorship, expand research skills, and help focus and refine your research path.

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Table.

Examples of population-based epidemiological studies that investigate stroke

Study name	Location(s)	Lead/coordinating institution	Year of inception
Longitudinal cohort studies			
Age, Gene, Environment, Susceptibility Study (AGES)	Reykjavik, Iceland	Icelandic Heart Association	11967
Atherosclerosis Risk in Communities Study (ARIC)	Forsyth County, North Carolina (NC); Jackson, Mississippi (MS), Minneapolis Suburbs, Minnesota (MN), and Washington County, Maryland (MD), United States of America (USA)	UNC-Chapel Hill	1987
Cardiovascular Health Study (CHS)	Forsyth County, NC, Pittsburgh, Pennsylvania, Sacramento County, California (CA), and Washington County, MD, USA	University of Washington	1990
Framingham Heart Study (FHS)	Framingham, Massachusetts, USA	Boston University	1948
Jackson Heart Study (JHS)	Jackson, MS, USA	University of Mississippi	1998
Multi-Ethnic Study of Atherosclerosis (MESA)	Baltimore, MD, Chicago, Illinois, Forsyth County, NC, Los Angeles County, CA, Northern Manhattan and Southern Bronx, New York (NY), St. Paul, MN, USA	University of Washington	2000
REasons for Geographic And Regional Differences in Stroke (REGARDS)	Southeastern USA (NC, South Carolina, Georgia, Tennessee, MS, Alabama, Louisiana, Arkansas) and participants from other states	University of Alabama at Birmingham	2003
Rotterdam Study (RS)	Rotterdam, Netherlands	Erasmus Medical Center	1990
Three-City Study (3C)	Bordeaux, Dijon, and Montpellier, France	Université Victor Segalen	1999
Stroke surveillance and population-based studies from regions with controlled referral patterns			
Brain Attack Surveillance in Corpus Christi (BASIC)	Nueces County, Texas, USA	University of Michigan	2000
Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)	Five-county region of Greater Cincinnati, Ohio/Northern Kentucky, USA	University of Cincinnati	1993
Northern Manhattan Study (NOMAS)	Washington Heights neighborhood, New York City, NY, USA	Columbia University	1990
Oxford Vascular Study (OXVASC)	Oxfordshire county, England, United Kingdom	University of Oxford	2002
Rochester Epidemiology Project (REP)	Twenty-seven-county region in MN, Wisconsin, USA	Mayo Clinic	1966
Stroke Investigative Research and Education Network (SIREN)	Eight centers in Ghana and Nigeria	University of Ibadan	2014
Cohort studies designed to focus on women's health			
Black Women's Health Study (BWHS)	Participants from every state in the USA	Boston University	1995
California Teachers Study (CTS)	CA, USA	City of Hope Cancer Center	1995
Iowa Women's Health Study (IWHS)	Iowa, USA	University of Minnesota	1986

Study name	Location(s)	Lead/coordinating institution	Year of inception
Nurses' Health Study (NHS), NHS II	17 states in the USA	Brigham and Women's Hospital (BWH), Harvard Medical School (HMS)	1976
Women's Health Initiative (WHI)	40 clinical centers in the USA	Fred Hutchinson Cancer Research Center	1991
Women's Health Study (WHS)	USA	BWH, HMS	1991