



HHS Public Access

Author manuscript

Neuroepidemiology. Author manuscript; available in PMC 2016 October 28.

Published in final edited form as:

Neuroepidemiology. 2015 ; 45(3): 221–229. doi:10.1159/000441105.

From Data to Action: Neuroepidemiology Informs Implementation Research for Global Stroke Prevention and Treatment

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Keywords

Comparative effectiveness research; Pragmatic trials; Developing country; Health inequities; Implementation research; Neuroepidemiology; Stroke epidemiology; Health policy development

Introduction

Neuroepidemiology, a term coined nearly half a century ago, has traditionally been defined as the study of the frequency, distribution, determinants, and outcomes of neurologic diseases in human populations. This definition however, highlights only the non-experimental and descriptive aspects of neuroepidemiology.[1] As a scientific field of study, neuroepidemiology now also includes experimental aspects that span the full spectrum of clinical and population science research encompassing fundamental discovery as well as

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Conflict of Interest Disclosure: None

Disclaimer:

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research into compelling questions and critical challenges around the translation of discovery science findings into health impact in populations with neurological disease.[1] The Global Burden of Disease (GBD) Study findings on stroke reported in this issue of the journal[2–6] and elsewhere[7–11] provide a wealth of data and insights to inform clinical and public health practice as well as guide health policy development. How do we tap into this wealth of data to inform actions that will maximize health impact?

In this review, we begin with an overview of the progress made in experimental and non-experimental neuroepidemiology over the past quarter-century with emphasis on evidence generation, critical appraisal of that evidence, and impact on clinical and public health practice at the national, regional, and global levels. Attention is then focused on implementation gaps which include identifying how best to scale-up evidence based treatments for neurological diseases for various global populations. Evidence gaps in biomedical research, stroke burden, clinical outcomes, and disparities between developed and developing countries are described. New directions in comparative effectiveness and implementation research are discussed as avenues for turning neuroepidemiological insights into action to maximize clinical and population health impact and to guide further biomedical research on neurological diseases. The review concludes with a call for rigorous evidence synthesis in neuroepidemiology and the design and execution of novel implementation and dissemination research studies that can lead to practice-based evidence that will underpin a bold new era of data-informed stroke prevention and treatment.

Progress and challenges in the last quarter-century

Over the last quarter-century, neuroepidemiology has matured and is now well-established as a fundamental clinical research approach. There have been significant developments in new statistical methods and study designs that have allowed new evidence generation in nearly all aspects of the distribution, prevention, treatment, rehabilitation and outcomes of neurological disorders. In addition, there has been accumulating knowledge about race/ethnic and sex differences in the distribution and determinants of neurological disorders in various countries and populations. Critical appraisals of that evidence, including systematic reviews and meta-analyses, have led to development of state-of-the art guidelines on the prevention and management of neurological disorders which, in turn, led to changes in policies aimed at reducing the burden of neurological disorders.[12] A recent example is proposed standards (STRONG checklist) for reporting incidence and prevalence studies in neuroepidemiology.[13]

As another example, in the United States, age-adjusted stroke rates have declined from the third to the fourth leading cause of death.[14;15] Stroke prevalence, however, has increased given the increased life span and aging of the population and stroke remains one of the leading causes of adult disability.[14] In part, decline in stroke mortality was because of decreased incidence, due to improvement in risk factor control, and decreased case-fatality, due to the rise of certified stroke centers improving the quality of evidence-based acute stroke care.[16;17] Epidemiological research in the United States has resulted in an improved understanding of the public health burden of stroke in high-risk groups, including African Americans and those residing in the southeast United States. Several community-

based and multicenter longitudinal epidemiological studies have helped address gaps in our knowledge of stroke epidemiology. Novel stroke risk factors have been identified, and these findings have helped guide interventions that may improve the health of the United States population and others around the globe. These findings may provide new insights into the prevention and treatment of stroke worldwide.

As part of the update to the Stroke Progress Review Group 2012, the Stroke Epidemiology and Risk Factors panel reviewed the state of NIH-funded stroke epidemiology research and summarized advances across several priority areas.[18;19] These areas include: (1) the development of common data elements (CDE); (2) linkages between epidemiological data and administrative data; (3) stroke trends; and (4) research training in epidemiology.[18] For example, data standards that include recommended CDE as well as case report forms, which could be used by epidemiologic studies, have been developed.[20–22] The National Human Genome Research Institute has developed the PhenX Toolkit, which provides standard measures related to complex diseases, phenotypic traits and environmental exposures relevant to epidemiological studies of stroke.[23–25] Furthermore, the NIH has also supported other activities including Quality of Life in Neurological Disorders (Neuro-QOL) funded by NINDS, the NIH Toolbox for the Assessment of Neurological and Behavioral Function and the Patient-Reported Outcomes Measurement Information System (PROMIS) that provide standardized validated self-report measures which incorporate measures for neurological disorders freely available to providers and practitioners. Several NIH funded grants are now linking population-based epidemiologic studies to Medicare data, enabling the identification of stroke without the difficulty and expense of medically verified stroke events.[26–29] Training opportunities in clinical research methodology and epidemiology had been increased through the broad array of NINDS research training and career development programs.[18;19]

Similar advances in neuroepidemiology have been made in the high income countries of Western Europe, Australia, New Zealand, Japan, as well as in low- and middle-income countries.[30–32] In Tanzania, for example, stroke incidence was assessed in two surveillance sites: Hai (rural) and Dar-es-Salaam (urban) from 2003–2006.[32] Individuals with stroke were systematically identified by community-based investigators and coordination with local medical center personnel. Crude annual stroke incidence rates were 94.5 per 100 000 in Hai and 107.9 per 100 000 in Dar-es-Salaam, but when age-standardized to the WHO world population, annual stroke incidence was 108.6 per 100 000 in Hai and 315.9 per 100 000 in Dar-es-Salaam.[32] To place these data in context, age-standardized stroke incidence rates in Hai were similar to those reported in developed countries, but those in Dar-es-Salaam were higher than figures from high-income countries.

Furthermore, Global Burden of Diseases (GBD) data for the sub-Saharan Africa (SSA) region showed that the amount of increase in the age-standardized ischemic stroke incidence for 1990 – 2010 ranged between 5.2% (South Africa) and 27.8% (Democratic Republic of Congo), and for hemorrhagic stroke the incidence ranged between 13.0% (The Gambia) and 45.7% (Burundi).[10;33] Thus, based on the limited available evidence, the incidence of stroke in Africa not only ranks among the highest globally, but its rate of increase is also significant compared to other world regions. Stroke is also the premier cause of

cardiovascular disability adjusted life years (DALYs) in SSA, rising from 5.9 million (39.5%) in 1990 to 7.8 million (52.0%) of CVD DALYs in 2010.[34] While there is paucity of data on the economic burden of stroke in SSA, a study of the cost of stroke care in Togo noted a direct cost per person of 936 Euros in just 17 days, which is approximately 170 times the average annual health spending of a Togolese.[35]

Thus, in sub-Saharan Africa, while modest yet important progress has been made in obtaining neuroepidemiologic data relevant for enhancing stroke outcomes overall, more studies are warranted. Ongoing studies like the Stroke Investigative Research and Educational Network (SIREN) Project may yield important new knowledge.[36] SIREN aims to identify the unique risk factors (genetic and environmental) linked to stroke occurrence, subtype, distribution and prognosis in SSA by evaluating 3,000 stroke case-control pairs at 9 sites in West Africa.[36] Furthermore, SIREN will also engage patients, caregivers, and local leaders about stroke prevention and treatment which will help promote better uptake of medical regimen, adherence, behavioral modification, and educate and sensitize the community to early presentation of stroke cases at home to allow for greater facilitation to hospitals for treatment. [36].

In spite of significant progress, there remain major knowledge gaps in many aspects of stroke epidemiology including elucidation of the determinants of stroke and stroke risk factor disparities by sex, race, and ethnicity; impact of unhealthy diets and the rise in physical inactivity, obesity, and diabetes; predictors of stroke recovery; and impact of vascular disease on cognitive aging and dementia. Among these, the three top priorities for future directions of stroke epidemiology recommended by the Stroke Progress Review Group 2012 included (1) improving the understanding of race and ethnicity in stroke disparities; (2) evaluation of the usefulness of health information technology as a tool for epidemiology research; and (3) translating knowledge from epidemiological studies into improved health.[18;19]

Continued support of epidemiologic stroke studies that monitor trends in stroke burden, fill gaps in knowledge, and discover new associations should be a high priority. Critically, we need to accelerate the translation of the results from epidemiology studies into improved health by informing evidence-based practice recommendations and clinical care, translating findings into behavioral interventions, and providing the fundamental preliminary data needed for randomized clinical trials.

In spite of this progress in the design, methodologies and analyses of stroke epidemiological studies and in knowledge gains, a number of unresolved issues and inconsistent findings in stroke prevention and management require further attention. From systematic reviews and GBD data, there are also deepening gaps between developed and developing countries in stroke research and burden.^{7, 8} For example, although the bulk of the global burden of stroke resides in low- and middle-income countries, the majority of research on and evidence for stroke prevention and management comes from developed countries.^{9, 10} Stroke incidence and mortality rates have been declining consistently over four decades in developed countries, but stroke incidence and mortality rates in developing countries are on the rise.⁸ Additionally, in every country examined, the absolute number of people affected, disabled

by, and/or who die from stroke annually is increasing.⁷ While the former is likely due to the lack of evidence for population-specific and culturally appropriate preventive and management strategies in developing countries,^{9, 10} the latter suggests that currently used primary stroke prevention strategies targeting primarily high cardiovascular risk individuals are not effective enough. Thus, new, more effective primary stroke prevention strategies are urgently needed worldwide.¹¹

Persisting Stroke Disparities

Health disparities in stroke and stroke care remain pervasive worldwide. Despite major initiatives at the national and sub-national levels to reduce and eliminate these disparities, they have remained remarkably persistent and in some settings have widened.[37] In the United States - where the elimination of health disparities was one of two overarching strategic health objectives for 2000 to 2010, and substantial declines in age-adjusted mortality rates occurred in both blacks and whites - the magnitude of racial and geographic stroke disparities substantially increased during that period.[37] These disparities have persisted in stroke mortality, morbidity, prevalence of risk factors, healthcare access, and in stroke quality of care.

Findings from NOMAS and other epidemiological studies have demonstrated racial and ethnic differences in stroke incidence. Increased annual stroke incidence was 2.4 fold among blacks and 2-fold among Hispanics compared to whites living in the same community. [38;39] Blacks in Cincinnati and Mexican Americans in Corpus Christi also have been found to have an increased incidence of stroke compared to whites.[40–42] American Hispanics not only have stroke more frequently, but they also have a greater risk of small vessel stroke (lacunar infarcts and intracerebral hemorrhage) and intracranial atherosclerosis.[43]

Potential explanations for these race-ethnic disparities include variations in risk factor potency, prevalence, and access to treatment arising from socioeconomic, environmental, and genetic factors.[44;45] For example, hypertension is a major contributor to black vs. white differences in stroke risk,[46] and underlying disparities in the prevalence of ideal cardiovascular health, including modifiable lifestyle behaviors and treatable health factors, are major contributors to differences in the incidence of stroke, MI and vascular death.[47] However, traditional risk factors contribute to less than half of the black-to-white racial disparities in stroke. The unexplained additional risk may potentially be attributable to other sources that require further investigation.[48] A recent large and robust case-crossover study in the US showed that acute infection disproportionately increases the risk of stroke death for non-Hispanic blacks and thus contributes to racial disparity in stroke mortality.[49] Reducing stroke disparities will require innovative approaches to improve cardiovascular health across all race and ethnic groups and specific interventions for addressing disparities.

Studies have documented disparities in access to acute stroke care, activation of 911 services, delayed arrival to the emergency departments, longer waiting times, and treatment delays in thrombolysis.[50] Moreover, secondary and tertiary stroke prevention programs are initiated during the acute hospital phase and may also demonstrate care disparities.

Decisions made about the use of antiplatelet medications, oral anticoagulants, hypertension control, statin treatment, diagnosis and control of hyperglycemia, the need for lifestyle management, and referral for rehabilitation services may demonstrate disparities by race, ethnicity, socioeconomic status or sex.

The Get With the Guidelines (GWTG)-Stroke program was developed by the American Heart Association/American Stroke Association to improve acute stroke performance by implementing evidence-based care. Over the last few years it has grown to include data from over 2 million stroke admissions from more than 1,600 United States hospitals. GWTG data have provided important insights into disparities in the quality of stroke care.[51] Moreover, adherence to evidence-based guidelines and quality improvement programs are a very effective way to minimize and eliminate acute stroke disparities. Eliminating stroke disparities will require multi-level interventions across multi-sectors that address not only individual stroke risk factors, but also the social and environmental conditions that disproportionately expose race-ethnic groups to elevated risk.

Gaps in Implementation Research in Stroke Prevention and treatment

The major scientific and technological advances in the detection, evaluation, treatment, and control of neurological disorders have not been matched by commensurate advances in factors that drive sustained implementation of evidence-based interventions in different practice settings.[52–54] Research advances have led to the development of tools to detect stroke and determine the underlying cause to inform treatment decision making. These advances have also been important in stroke drug development and in stroke treatment and prevention protocol development. These strategies have been instrumental in identifying the major challenge areas but have provided limited information on how individual hospitals and practices can adopt protocols and improve the prevention and treatment of stroke in practice.

The first national stroke registry was established in Sweden in 1994, and since then many other similar registries have been developed. A recent review identified the existence of 28 national stroke registries in 26 countries.[55] The two major approaches to monitoring the quality of care with a registry were: 1) traditional registries, which provide the most comprehensive data, but are resource-intensive to run and have optimal coverage when mandatory; and 2) administrative database linkage, which is cheaper with greater coverage, but often lacks detail and is feasible in only some jurisdictions. Almost all national stroke quality registers are located in high or middle income countries.

Within the United States, stroke quality improvement initiatives such as the GWTG-Stroke and the Joint Commission Certification levels of stroke certification have sustained and improved inpatient stroke quality measure compliance and in turn improved stroke outcomes and possibly prevention of recurrent stroke in the hospitals that have adopted the program. [56] GWTG not only informs hospital system and healthcare practitioners of the accepted guidelines for stroke care, it also helps to organize stroke care at hospitals, and works to identify barriers to optimal care through data collection, analysis, feedback, and process improvement. GWTG-Stroke has not been widely adopted outside of the United States.

Taiwan and Brazil are the first and second countries with hospitals to adopt the key indicators identified in GWTG and publish initial information on the outcomes.[57;58] Adopting GWTG-Stroke requires tailoring regarding the quality indicators that are collectible, how frequently to measure a given indicator, and having the opportunity and resources to intervene.

Despite these efforts, there is little information available regarding stroke and actionable targets for improvement in many parts of the world, particularly in low and middle-income countries. There has also been slow adoption and limited tailoring of quality improvement programs, and slow utilization of available tools to advance stroke detection, treatment, and prevention. Although these examples of successful implementation of knowledge into practice are excellent, they are the exceptions. For example, despite these advanced state of stroke care in the Taiwan and Brazil studies, there is limited use of further testing that can be useful in correctly identifying the cause of stroke and better treatment. In general, we also lack data on how to turn clinical insights from research discoveries into sustained population health impact.[59;60]

Turning data into action-An Agenda for Implementation Research

Over a decade ago, the Institute of Medicine's Clinical Research Roundtable issued a report that showed that one of the 'bottlenecks' in turning data from clinical trials into actions leading to widespread improvements in health was the lack of research that enables findings of efficacy from such trials to produce broad, appropriate, and beneficial use in populations. [61] Typically, these trials are nearly always conducted under conditions tightly controlled by investigators and among narrow, relatively homogeneous patient samples. While this translational bottleneck has analogous obstacles to those that delay translation of basic research into efficacy trials in humans, what is markedly different is the type of scientific disciplinary expertise necessary for translation from those efficacy trials into population health, as well as the type of research infrastructure needed for this research, and the very underdeveloped funding streams for this effort. In the past decade, the field of implementation science has emerged, encompassing multi-disciplinary research requiring social science, behavioral science, public health, and health services research expertise and methods. At the same time, comparative effectiveness has emerged as a new term for an old concept, which is that as new evidence is developed over time about efficacy of new advances in diagnosis and treatment, the comparator that is relevant for clinical decision-making is the relative benefit of the new advance to existing standard approaches, rather than to placebo.[62]

Both comparative effectiveness and implementation research have been invigorated in the last decade by new policies and funding streams, a consequence in the United States of the necessity and urgency of restraining healthcare costs that have continued to rise much more rapidly than the country's economic growth. It was the United States Congressional Budget Office that first produced a comprehensive report on the fledgling vision of comparative effectiveness and its potential contribution to rigorous evaluation of alternatives in healthcare.[63] Similarly, the Affordable Care Act led to funding that established the Patient-Centered Outcomes Research Institute (PCORI) and to the Centers for Medicare and

Medicaid Services portfolio of funding for scaling up evidence-based healthcare delivery innovations. It also led to development of targets for the proportion of the Medicare population covered under radically different payment policies that incentivize meeting a priori targets for quality of care and reducing unnecessary healthcare utilization (“value-based care”).[64] At the same time, the introduction of these changes holds great promise for addressing racial and ethnic disparities in healthcare, not only by improving access as through expanded coverage under the Affordable Care Act, but also by enabling testing and scale-up of innovative models of care that may be more highly effective in vulnerable populations and which cannot be paid for under prevailing fee-for-service payment structures.

There are well-characterized approaches for development of practice guidelines based on systematic reviews and structured group judgments of the extant literature that national and international stroke associations, other professional societies, and the Institute of Medicine have pioneered.[65;66] Stroke is one of the most highly-prevalent and devastating neurological conditions compared to other neurological disorders, there has been a substantial body of research to develop new treatments, particularly in acute stroke care but increasingly in primary and secondary prevention and in rehabilitation. This makes stroke a condition that is ripe for comparative effectiveness and implementation research, to ensure that the new knowledge generated from these trials of stroke therapeutics and prevention approaches indeed result in the population health benefits that were the ultimate goal of the societal investment in biomedical research on causes and consequences of stroke. An example of a lag in translation of high-quality evidence into practice is multi-disciplinary acute stroke units. Although compelling evidence from several randomized trials demonstrate they reduce mortality, improve outcomes and confer a clear protective effect in those facilities conducting the trials,[67] uptake and diffusion of these effective strategies by the stroke teams in acute care hospitals has been very slow.. Delays in translation of efficacious treatment approaches into widespread practice mean lost lives and increased morbidity.

Another prime example of the importance of implementation research in stroke is secondary stroke prevention. There is substantial evidence as to what contributes to risk of recurrent stroke and what can prevent recurrent stroke: control of high blood pressure, antithrombotic medication, LDL control, smoking cessation, and appropriate diet and levels of physical activity. Yet, hypertension control in the United States remains suboptimal at less than 50%, [68;69] and in several studies, only one-third of individuals known to be at high-risk for stroke had achieved control of blood pressure and LDL one year after identification as high risk.[70] Those with lower access to health care and language and literacy barriers have worse stroke risk factor control and higher recurrent events. In response to this, the NINDS has invested in an initiative to produce evidence for innovative approaches to primary and secondary stroke prevention in vulnerable populations.[71]

To leverage the current body of neuroepidemiology research into action that yields demonstrable benefits in population health and reduction or elimination of health disparities, national goals or targets for specific, high-prevalence neurologic conditions such as stroke need to be set, then a roadmap developed for achieving those targets, based on research and

research-to-practice gaps in knowledge and by fostering handoffs along the translational spectrum among key stakeholders. The process should engage multiple stakeholders including public and private sponsors of research together with academic, community, delivery system, and public health representatives and decision-makers. A mechanism for periodic assessment of progress relative to those goals is essential.

Conclusions

With new and constantly evolving methods of neuroepidemiological studies, their wider use and increasing implementation across the globe, neuroepidemiology is expected to play a central role in the translation of evidence on the frequency, distribution and determinants of neurological disorders to clinical and public health practice in order to maximize individual patient and population health impact.[72;73] However, turning descriptive, analytical and experimental neuroepidemiological data into clinical and public health action for population health impact requires quality data, rigorous evidence synthesis, and the design and execution of rigorous dissemination and implementation research that incorporate the dynamics and complexities of the health care system context in which interventions are delivered.[74;75] There is an urgent need for research that can lead to evidence-based recommendations for practice. Important among these are comparative effectiveness studies and large, simple, pragmatic trials that will generate practice-based evidence. Concerted, coherent, and timely translation of the knowledge generated into evidence-based recommendations for practice with corresponding changes in health policy at the governmental levels will be crucial. So will early and sustained engagement of multiple, diverse stakeholders including public and private sponsors of research together with academic, community, delivery system, and public health representatives and decision-makers in order to reduce the burden of stroke worldwide.

Acknowledgments

The authors thank Drs. Barbara Vickrey, Michael Engalgau, Emmanuel Peprah, and Helena Mishoe who provided critical review and constructive input on an earlier version of this document.

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