Ancel Keys Lecture
Adventures (and Misadventures) in Understanding (and Reducing) Disparities in Stroke Mortality

George Howard, DrPH

One of the 2 key goals of the Healthy People 2010 statement, the guiding document for the United States Department of Health and Human Services, is to “eliminate health disparities among different segments of the population” by the year 2010.1 The US Congress has by law directed National Institutes of Health (NIH) to specifically define health disparities to include the components:

- Minority health research and related activities.
- Rural health research and related activities.
- Research and other activities related to the socioeconomically disadvantaged in the urban setting.2

For brevity, we focus on a review of the magnitude of the disparities in stroke of only the first 2 of these disparities: review progress in reducing these disparities, and assess barriers and opportunities to reduce these disparities.

Minority Health Research and Related Activities
Racial differences in stroke mortality are the most well-known and well-documented of the stroke disparities.3-5 Among non-Hispanics aged between 45 and 64 years, in 2009, there were 4359 deaths from stroke and an age-adjusted death rate of 48.9 per 100 000 in blacks, whereas there were 9994 deaths and a death rate of 16.3 per 100 000 in whites; this represents a 3-fold difference in death rates.6 There would have been ≈3000 fewer deaths for blacks in this 20-year age range if they had the mortality rate of whites (4359×(16.3/48.9)=1424 projected deaths for a reduction of 2935 deaths). If the case-fatality rate is 20%, then these 3000 (3000/0.2=15 000) =2.1 billion dollars annually (assuming a $140 000 cost of stroke).7

The racial disparity in stroke mortality has been remarkably persistent, where between 1949 and 1951 the nonwhite (primarily blacks)/white stroke mortality ratio was 1.63 for men and 1.92 for women (reported in the very first volume of Stroke).8 Using CDC WONDER,8 for ages ≥45 years, we observed a remarkable 37% decline in the age-adjusted cerebrovascular disease mortality between 1999 and 2009 (1999: 173.2/100 000—2009: 108.6/100 000). Although there was a decline for each race/ethnic group, the cerebrovascular disease death rates (International Classification of Diseases-Tenth Revision: 160-169) are strikingly higher for blacks than for whites and marginally lower for Hispanics, Native Americans, and Asians than for whites (Figure 1 Left). Although the cerebrovascular death rates are falling for both whites and blacks, it is falling consistently faster for whites, resulting in a 26% increase in the black/white mortality ratio from 1.36 in 1999 to 1.45 in 2009 (Figure 1 Right); hence, although cerebrovascular deaths are falling for both blacks and whites, with the exception of the past 2 years (where there have been minor declines in the black-to-white disparity in stroke), the magnitude of the black-to-white disparity in stroke is consistently and rapidly growing. Relative to whites, declines in cerebrovascular deaths for Asians (ratio of 0.89 in 1999; ratio of 0.83 in 2009) and Native Americans (ratio of 0.87 in 1999; ratio of 0.79 in 2009) seem marginally faster than in whites, whereas declines for Hispanics (ratio of 0.77 in 1999; ratio of 0.77 in 2009) are at approximate a similar magnitude as whites (Figure 1 Right).

During the past 15 years, National Institute for Neurological Disorders and Stroke (NINDS) has funded observational epidemiological studies that have provided valuable insights to the causes of the racial disparities in stroke. Despite the racial disparity in stroke mortality being well described in publications since the mid-1970s, as late as the mid-1990s, it was not clear whether the higher mortality among blacks was attributable to a higher incidence of stroke or a worse case fatality from stroke. Stroke surveillance studies in racially diverse communities addressed this knowledge gap when in 1998 the Northern Manhattan Stroke Study (NOMAS) reported that the black/white incidence ratio was 2.4,9 a finding supported by the an estimated 2.0 black/white incidence ratio in the 2004 report of Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS).10 These findings from specific communities have subsequently been supported by national data on black–white differences in stroke incidence.11 These data seem to suggest that it is critical to guide interventions to reduce the black-to-white disparities to primarily focus on incidence of incident stroke events through primary (or primordial) prevention, rather than efforts to reduce case
fatality through improved stroke treatments. However, temporal increases in the magnitude of the black-to-white disparity may potentially be attributed a more rapid access by whites (and non-Southerners) to acute stroke care units that shown to improve outcomes after stroke,12 and as such secondary attention could potentially be focused on stroke care to reduce the black excess in stroke mortality.

Simultaneously, NOMAS estimated the Hispanic/white stroke incidence ratio to be 2.0 for Hispanics in Manhattan,9 a finding supported for Mexican Americans in the Brain Attack Surveillance in Corpus Christi (BASIC) study estimating a Hispanic/white incidence ratio of 2.00 for ages 45 to 59, 1.57 for ages 60 to 74, and 1.13 for ages >75.13 The paradox of higher stroke incidence, but lower stroke mortality (Figure 1 Right), among Hispanics is potentially related to misreporting of ethnicity in the vital statistics system, underscoring the importance of these targeted surveillance studies using more standard definition to identify disparities that might well otherwise go undetected. However, it has been suggested that reporting of Hispanic ethnicity in the vital statistics is relatively good,14 a finding supported by concordance (sensitivity, specificity, and accuracy) in access of 95% between self-reported race and vital statistics among 480 deaths in the BASIC study,13 making it somewhat unlikely that misreporting totally explains this paradox. Alternatively, there is also the possibility that Hispanic–white ethnic differences in stroke mortality are also confounded with Hispanic–white geographic differences in stroke mortality. Specifically, between 2007 and 2009, there was a sufficient Hispanic population for the CDC to report smoothed Hispanic mortality rates in 635 of the 3141 (20%) counties in the United States, whereas they reported smoothed white mortality for 3115 of the 3141 (99%) of the counties (smoothing of rates making the reporting of county-level mortality more reliable).16 New York County (largely Manhattan, the location of the NOMAS) had a stroke mortality of 39.2 per 100 000 for Hispanics, which was in the ninth percentile of counties reporting Hispanic mortality; however, the stroke mortality for whites was 36.7 per 100 000, the fifth lowest of the 3115 counties reported (ie, in the 0th percentile of counties reporting white mortality). Hence, NOMAS was conducted in a county with a low relative Hispanic mortality compared with other regions, but New York County has even lower relative white stroke mortality (in fact, white stroke mortality in the city of New York has lowest white stroke mortality in the nation, with Kings County a rank of 1, Richmond County a rank of 2, Queens County a rank of 3, New York County a rank of 5, Bronx County a rank of 7, and Nassau County a rank of 15 of the 3115 counties reporting white mortality). Likewise, Nueces County, TX (the location of the BASIC study) has a Hispanic stroke mortality of 95.1 per 100 000, which is in the 88th percentile of counties reporting Hispanic mortality, whereas the white stroke mortality is 86.0 per 100 000, which is in the 53rd percentile of counties reporting white mortality. Hence, another possible explanation of the paradox of high stroke incidence but lower stroke mortality is that NOMAS is being conducted in a county with low Hispanic mortality but strikingly lower white stroke mortality, whereas the BASIC study is being conducted in a county with high Hispanic mortality but average white stroke mortality.

Because there are few sources on temporal changes in stroke incidence, the causes for the decline in stroke mortality, and impact of these declines on racial disparities, remain a mystery. Early reports from predominately white communities have suggested only a modest decline in stroke incidence that is likely insufficient to account for the dramatic declines in stroke mortality.17,18 Recent reports from GCNKSS have fueled this mystery with indications that stroke incidence rates seem to be falling for whites but not for blacks, potentially contributing to the 35% increase in the black/white mortality ratio between 1999 and 2007.19 The decline in stroke mortality was recognized as one of the Ten Great Public Health Achievements for the previous century20; however, we cannot expect to sustain the decline in stroke mortality without understanding its cause, again underscoring the importance of the sustained funding for stroke surveillance studies.
Although surveillance studies have provided insights to the changing pattern of stroke risk (incidence, case fatality, and mortality), surveillance studies do not have data on risk factors before the stroke event and as such are limited with respect to providing insights to guide interventions to reduce disparities in stroke incidence. Longitudinal cohort studies that are complementary to surveillance studies can address this knowledge gap and include studies such as the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study, the longitudinal cohort in the NOMAS, the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), and the Multi-Ethnic Study of Atherosclerosis. As surveillance studies have shown the importance of racial disparities in stroke incidence, reducing the disparity in stroke must be through primary (or primordial) prevention efforts to reduce stroke incidence disparities, with treatment of stroke playing a secondary role in efforts to reduce racial disparities in stroke. Although summarizing all findings from longitudinal studies focused on disparities in stroke incidence is beyond the scope of this report, some of the findings particularly pertinent to guiding interventions to reduce disparities are provided herein.

The National Health and Examination Survey (NHANES) study estimated approximately one third of the excess stroke incidence risk in blacks could be attributed to disparities in traditional risk factors (hypertension, diabetes mellitus, smoking, etc). However, this effort was limited by a small number of blacks (1362) and by the lack of physician adjudication of stroke events. The REGARDS study recently updated this effort, finding that the racial disparity in incidence is primarily below the age of 65 years, and in this age range approximately one half of the racial disparity in stroke incidence is attributable to traditional risk factors (ie, those in the Framingham Stroke Risk Profile).

There are major implications of this observation to guide interventions to reduce racial disparities. Specifically, because much of the disparity is attributable to disparities in the prevalence of these risk factors at the baseline visit, efforts to reduce the racial disparity through these risk factors must focus on reducing the disparities in risk factor prevalence (ie, eliminating the excess prevalence of hypertension and diabetes mellitus in blacks) rather than improved treatment of prevalent risk factors. Noting that a higher prevalence is the product of some combination of a higher incidence or lower case fatality, it is almost certain that the racial disparities in risk factor prevalence are attributable to racial disparities in risk factor incidence because (1) the alternative explanation of a lower mortality of blacks with the risk factors reducing the prevalence ratio seems unlikely and (2) it has been shown that blacks have a higher incidence of hypertension (the single most potent risk factor for stroke) than whites at all ages ≤75 years.

Hence, to reduce the black-to-white differences in risk factor prevalence, we must reduce the black-to-white differences in the incidence of these traditional risk factors. Efforts to go upstream to address disparities in the incidence of stroke risk factors will be key to address the half of the disparity attributable to these traditional risk factors.

There is also the opportunity to reduce racial disparities in stroke incidence by a better understanding of pathways that do not involve these traditional risk factors. These pathways may include (1) racial differences in the impact of risk factors (eg, that similar elevations of blood pressure may impart more risk in blacks than whites), (2) lack of adequate quantification of known risk factors (ie, residual confounding), (3) nontraditional or novel risk factors, and (4) measurement error of the known risk factors. REGARDS and other studies are focusing efforts to advance the understanding of the potential role of each of these pathways, with promising early findings to provide insights to target to reduce racial disparities. Examples of findings include (1) documentation that blacks are actually more aware and more likely to be treated for hypertension, but that the treatment is much less likely to result in achieving blood pressure goals, (2) the potential that risk factors may, in fact, have a differential impact in blacks and whites, for example, with elevated levels of systolic blood pressure being associated with approximately a 3-fold larger increase risk of stroke in blacks than in whites, (3) that after control for blood pressure levels, racial differences in duration of hypertension could be playing a substantial role in differential stroke risk, and (4) numerous novel risk factors could be contributing to racial disparities in stroke incidence, including disparities in the prevalence of stroke symptoms, racial differences in awareness and treatment of atrial fibrillation, racial differences in stroke severity arising from population stratification introduced through a genetic differences in hypertension or other risk factors, differential impact of markers of inflammation, including C-reactive protein, racial differences in the age of menopause, the role of diet, including differences in fish consumption, and systemic infections, such as tooth loss. Although much work remains, understanding these new pathways that potentially contribute to racial disparities in stroke incidence is a key first step to guiding the interventions to reduce this immense public health burden.

In conclusion, on racial/ethnic disparities, although stroke mortality is declining, the magnitude of black-to-white disparity in stroke mortality is consistently and rapidly increasing. In the past 15 years, NINDS–funded surveillance studies have documented that the black-to-white disparity in stroke mortality is primarily attributable to disparities in stroke incidence and have also documented substantial Hispanic-to-white disparities in stroke incidence (despite the lack of disparities in stroke mortality). NINDS–funded longitudinal cohort studies are rapidly accruing data, and substantial contributions to the understanding of the black-to-white disparity in incidence are in process; however, continued investments in surveillance studies and new cohort studies, including Hispanics, would help to clarify whether the Hispanic-to-white disparity in incidence remains.

Rural Health Research and Related Activities

Despite NIH explicitly defining rural health as a focus of disparities, and despite acknowledgment of opportunities for rural epidemiology of chronic diseases, to the knowledge of the author there are only a handful of articles contrasting stroke risk (mortality, incidence, or prevalence) for the United States in urban versus rural areas. A review of stroke in rural areas and small communities offered a single publication documenting a 1.45x higher prevalence of stroke in rural instead of urban areas (the data were provided in a table, with no comment in the text). Recently, Sergeev reported a rural/urban mortality
ratio of 1.37 for states outside the Stroke Belt between the years 2000 and 2006. There seems to be no report of urban versus rural differences in stroke incidence.

The CDC WONDER also provides the opportunity to assess urban–rural differences in stroke using the National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme, which scales counties on a 6-point scale from large central metro (most urban) to noncore (most rural). Estimates of stroke mortality for the non-Hispanic white (population restricted to avoid confounding with race) population aged >45 years is shown in Figure 2, where for early years (1999–2003) there seems to be little differences in stroke mortality for the 2 most urban classifications (Large Central Metro and Large Fringe Metro); however, after this period there seems to be a less rapid decline in the large fringe metro regions relative to the large central metro regions resulting in ≈5% increase in their relative risk. During that same period, 1999–2004, the medium metro areas showed pattern of a relatively constant 6% to 7% excess risk relative to the large central metro regions; however, since that time the relative risk in these regions also seems to be steadily increasing to a 13% excess. There was a similar pattern of increases for the 3 less rural classes (small metro, micropolitan, and noncore) that have a risk of ≈15% higher than the large central metro regions, but even larger increases to a 21% excess for the small metro regions and to 31% excesses for the micropolitan and noncore regions. Hence, although the magnitude of the higher stroke mortality in more rural regions was stable between 1999 and 2004, since that time the disparity seems to be increasing, with more rapid increases among the more rural areas. Secondary analysis, including all race-ethnic groups, showed similar patterns (data not shown). With the potential that rural–urban disparities in stroke potentially increasing, there is much work remaining in this area.

However, in a closely related area, there has been a well-documented geographic disparity in stroke mortality, specifically a higher stroke mortality in the Southeastern region of the United States that has been documented to exist for more than a half-century. The average stroke mortality is ≈20%
to 25% higher in the Stroke Belt than the rest of the nation; however, there is substantial heterogeneity in stroke mortality risk both in and out of the region, and stroke mortality for specific regions (such as the buckle of the Stroke Belt along the coastal plain of North Carolina, South Carolina, and Georgia) is as much as 300% higher than the lowest risk regions in the nonbelt (New York City, Miami, etc.). The pattern of stroke mortality in the Stroke Belt and non–Stroke Belt is shown in Figure 3 for non-Hispanic whites (to avoid confounding with race). Although there have been dramatic declines in stroke mortality in both regions, the excess stroke mortality has been nearly constantly 20% higher in the Stroke Belt region during this entire observation period (data not shown).

The NINDS–funded REGARDS study has a coprimary focus on advancing the understanding of the causes of the Stroke Belt. Initial examination of regional differences (ie, Stroke Belt versus non–Stroke Belt) in incidence was nonsignificant1; however, additional analyses on the county level are needed to evaluate the relative contributions of regional differences in stroke incidence versus stroke case fatality. REGARDS also documented that the Stroke Belt region also has a more rapid rate of cognitive decline, suggesting that more global measures of cerebrovascular health may also be affected by factors in the region.45 Before REGARDS, there were few data describing geographic disparities in the distribution of risk factor prevalence that may be contributing to the geographic disparities in incidence,6,47 primarily reporting a higher prevalence of hypertension in the region.48,49 Data from REGARDS confirmed the geographic disparity in hypertension and noted a larger geographic disparity in the prevalence of diabetes mellitus; however, again the relatively small disparities in these traditional risk factors may not be sufficient to account for the disparities in incidence (suggesting other factors are playing a role).50 REGARDS is currently investigating potential causes of the geographic disparities in traditional and novel risk factors, including less access to care,51 regional differences in the age of menopause (with the Stroke Belt having an average age of menopause 10 months earlier than the rest of the nation),52 a lack of smoking differences in whites and lower smoking exposure for blacks,52 lower intake of nonfried fish and higher intake of fried fish,37 a lower intake of fiber, potassium, magnesium, and calcium, but a higher intake of cholesterol, for men,53 and higher markers of inflammation and tooth loss because of gum disease54; however, there was a 10% lower use of aspirin for prophylactic use in the region.54 As such, REGARDS is well underway in assessing geographic differences in prevalence of nontraditional risk factors and is poised to perform mediation analysis to assess their role in the excess stroke risk in the region.

In summary of geographic disparities, although the NIH has focused on rural–urban differences in their definition of disparities, little work has been performed to assess such disparities in stroke. More work has been performed on the related geographic disparity of higher stroke in the southeastern region of the United States. Data from REGARDS suggest a higher stroke incidence in the region that is contributing some, but not all, of the geographic disparity in stroke mortality. There are sizable differences in the distribution of traditional and novel risk factors, but additional work is required to assess the relationship of the geographic differences in risk factors to the geographic disparities in stroke risk.

**Conclusions**

Although deaths from stroke are rapidly declining, the black-to-white disparity in stroke risk is increasing, and geographic disparities in stroke seem to be stable or increasing. There is solid progress in understanding the causes of the racial disparity in stroke risk, and this information holds promise to guide interventions that may decrease the racial disparity. In addition, more work is certainly warranted to better understand the potential stroke disparities in the Hispanic population, the largest US minority group. The focus of NIH on geographic disparities has been on urban–rural differences, an interesting area that has largely not been investigated for stroke. However, substantial efforts are underway to better understand geographic disparities associated with the Stroke Belt. This disparity seems to be at least partially attributable to increased incidence of stroke in the region, with this increase only being partially attributable to traditional risk factors. More work is needed to better understand the role of nontraditional risk factors or other pathways that could contribute to this substantial disparity.

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None.

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