DECODING STROKE DISPARITIES: ZIP CODES, COLOR CODES, AND EPIGENETIC CODES

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ABSTRACT

Despite decreases in overall stroke incidence and mortality in the United States, racial and ethnic disparities continue unabated. Of note, the long-standing disproportionate burden of stroke on African Americans compared to other racial and ethnic groups persists, and national projections indicate this toll will likely worsen over the next decade. Why have we not been able to bend the stroke disparities curve for African Americans? Well, this is mainly because traditional stroke risk factors, such as hypertension, diabetes, etc., account for just half of the Black vs. non-Hispanic White stroke disparity. As such, there is increasing interest in evaluating understudied factors like upstream social determinants of health, including geography, psychosocial stress, and environmental pollution; identifying potential mediators; and testing multilevel interventions to address them. This paper highlights emerging avenues that may help decode the excess stroke risk in African Americans, focusing on zip codes, color codes, and epigenetic codes.

INTRODUCTION

Stroke is a leading cause of death, disability, and dementia in the United States, thereby representing a major national public health threat (1). Stroke also exacts major costs in lost productivity to individuals, communities, and societal economies (1). Beyond its devastating medical and economic consequences, stark disparities in stroke incidence and mortality rates exist along racial, ethnic, and socioeconomic lines (2). Indeed, racial and ethnic minorities tend to have worse stroke risk factor control, less access to evidence-based acute

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stroke treatments, and poorer stroke outcomes compared to their non-Hispanic White counterparts (3). Fortunately, over the last three decades, due to better risk factor screening and treatment, there has been a welcome overall drop in stroke incidence and mortality rates in the United States (3). However, racial, ethnic, and regional disparities persist, especially in individuals of African ancestry who have among the highest stroke incidence and mortality rates worldwide, and projections suggest that these disparities will worsen over time (3,4).

An important distinction is often made between health inequities (differences in barriers that prevent individuals from attaining their optimal health potential) and health disparities (differences in health care processes and outcomes) (5). Overcoming health inequities necessitates addressing the social determinants of ideal health. These social determinants represent the milieu in which people live, learn, work, and play that influence a broad swath of health perils and prognoses (6). When it comes to the intersection of social determinants and cerebrovascular health, the emphasis up till now has largely been on improving the quality of stroke care (6). However, while it remains unclear as to which of the social determinants most strongly influences cerebrovascular health, it is increasingly clear that practitioners, policy makers, and public health officials need to be focused more on the upstream social determinants, especially those that fall under the category of Community and Social Context (6). Under the rubric of Community and Social Context are issues such as social integration, support systems, community engagement, discrimination, and psychosocial stress (6). In this article, I discuss the intersection of race, social determinants, and excess stroke risk in African Americans, by discussing the differential influence of zip codes, color codes, and epigenetic codes on stroke outcomes.

STROKE RISK BY RACE AND ETHNICITY IN THE UNITED STATES

For over five decades, people of African ancestry have experienced the highest rates of stroke prevalence, incidence, recurrence, and mortality in the United States (2,3). Despite a recent welcome drop in stroke incidence and mortality rates, differences in stroke rates between African Americans and other racial/ethnic groups are no better than they were fifty years ago (2,3). Indeed, more robust declines in

mortality rates among non-Hispanic Whites compared to their African American counterparts may have broadened the existing racial disparity in stroke mortality (2,3). Specific data show that the age-adjusted incidence in the United States of first ischemic stroke per 1,000 is 0.88 in White individuals, 1.91 in Black individuals, and 1.49 in Hispanic individuals (7). Even more worrisome, based on future U.S. projections of stroke occurrence, it is anticipated that there will be a further widening of the current Black–White stroke prevalence gap due to a further increase among Black men and women (2-4).

UNEXPLAINED EXCESS RISK OF STROKE IN AFRICAN AMERICANS

It is well known that the rates of the premier stroke risk factors, such as hypertension and diabetes, substantially differ by race and ethnicity (2-4). For instance, African Americans carry twice the odds of inadequately controlled blood pressure, are diagnosed with hypertension at an earlier age, and have more severe hypertension versus White individuals (5). Nonetheless, only half of the excess stroke risk seen among African Americans can be explained by just the greater presence of conventional stroke risk factors (8). Several hypotheses have been proposed for the yet unexplained additional risk of stroke observed among African Americans compared to non-Hispanic Whites (Table 1) (8). For example, with the first hypothesis suggesting a differential impact of the same level of a given risk factor by race, data from the REGARDS study provide some support to this notion. The REGARDS investigators observed that after the adjustment for several confounders, a 10 mm Hg difference in systolic blood pressure was associated with an 8% (95% CI, 0%–16%) increase in stroke risk for non-Hispanic Whites, compared to a rise in stroke risk of 24% (95% CI, 14%–35%) for Blacks (9). For the second hypothesis suggesting a contribution of fluctuations in a given risk factor over time, it's been noted that type 2 diabetes rates have been rising at a steeper pace among African Americans versus non-Hispanic Whites. In an analysis of nationwide data among hospitalized ischemic stroke patients in the United States, we found that over a decade, the prevalence of diabetes increased from 18.7% to 26.9% among non-Hispanic Whites versus 24.3% to 41.1% among Black individuals, with significantly higher odds of diabetes comorbidity among Black persons (odds ratio of 1.38, 95% CI, 1.35–1.41) (10).

TABLE 1
Leading Hypotheses for the Unexplained Excess Risk of Stroke in African Americans (8)

Hypothesis	Description
1	• Differential impact of risk factors based on race such that the presence of certain vascular risk factors may have a greater impact on Blacks than non-Hispanic Whites. ○ For example, a potentially higher impact of elevated systolic blood pressure on stroke risk among Blacks than Whites.
2	• Incomplete assessment of traditional risk factors with failure to capture crucial aspects. ○ For example, not fully capturing the duration of vascular risk factors or number/degree of fluctuations over time.
3	• Novel or emerging risk factors such as psychosocial factors, environmental pollution, dietary factors, vascular biomarker profiles, and inflammation. ○ These entities may exert racially driven independent effects or interact with traditional risk factors to potentiate or attenuate impact on stroke risk.
4	• Measurement error in predictive factors in various models.

For the third hypothesis, the influences of biological and genetic factors are crucial to consider. It is plausible that the higher rates of hypertension and diabetes seen in African Americans may in part be driven by genetic or inflammatory factors, which might be amenable to modification to improve stroke outcome (11). First, it has been shown that Black individuals have higher levels of inflammatory markers compared to other racial and ethnic groups, including C-reactive protein (CRP) and interleukin (IL)-6 (11). Second, psychosocial stress appears to raise susceptibility to stroke and poor stroke outcomes (Table 2) (12-19). However, a methodological challenge is that the effects of psychosocial stress can vary widely by type of stressor, duration of stress, unpredictability of stress, timing of stress, social environment, and genetics (17). Moreover, a relatively understudied, yet potentially pervasive, type of psychosocial stressor with regard to stroke risk is the experience of discrimination. Experiences of discrimination have been linked to greater presence of traditional cardiovascular risk factors as well as neurobiological mediators of vascular risk (20-23). Heightened cardiovascular and inflammatory responses to psychological stress predict raised blood pressure levels over ensuing years (22,23). According to psychosocial stress models of health disparities, racial and ethnic minorities in the United States experience greater exposure to perceived discrimination (20-23). A key question for future investigation is whether racial differences exist in the susceptibility and/or resilience to psychosocial factors, especially perceived discrimination, and may be harbingers of stroke.

TABLE 2
Links Between Psychosocial Factors and Stroke Risk or Outcomes (12-19)

Factor	Process	Description
Psychosocial Stressors	Mechanisms	• Stress has been related to stroke risk through the chronic stimulation of bone marrow to elaborate molecules that are central to the occurrence of vascular inflammation. • Perceived discrimination and inequalities in social status have been related to an increase in stroke risk via stimulation of the sympathetic nervous system and dampening of the parasympathetic nervous system. • Psychosocial factors may exert potentiating, moderating, confounding, or interacting influences on conventional risk factors for stroke such as hypertension, diabetes, and dyslipidemia.
	Epidemiology	• Psychosocial stress raises stroke risk by 30%, while depression boosts stroke risk by 35%. • A combination of prior stroke and depression has been linked to higher all-cause mortality compared to the presence of either condition alone, and the existence of post-stroke raises odds of dying from a stroke by 35-fold. • African Americans with low income plus combined depressive symptoms or stress have the highest risk of cardiovascular disease and stroke. • Per a systematic review of the literature and meta-analysis, perceived psychosocial stress is independently related to higher stroke risk.

GOING SOCIAL TO EXPLAIN EXCESS STROKE RISK IN AFRICAN AMERICANS

Zip Code (and Other Social Determinants)

Increasing evidence suggests that an individual's place of residence might play an important role in their risk for and outcomes of stroke (24,25). The REGARDS study, which sought to understand the reasons for racial and regional differences in stroke risk in the United States, evaluated independent relationships between key social determinants of health and occurrence of stroke in African Americans and non-Hispanic White Americans (26). The cohort comprised 55.4% women and 40.4% Blacks. Median follow-up was 9.5 years (IQR 6.0, 11.5). Table 3 displays the associations between the various social determinants and stroke risk (26). Poverty in an individual's zip code was one of the top stroke risk contributors. In fully adjusted models, among individuals <75 years old, risk of stroke increased as number of social determinants of health rose (26). Compared to participants without

TABLE 3

Various Social Determinants of Health and Risk of Stroke in the REGARDS Study (26)

Social Determinant	HR*** (95% CI***)	P-value
Black race	1.34 (1.20, 1.48)	< 0.0001
Low level of education	1.32 (1.14, 1.52)	0.001
Low level of annual household income	1.59 (1.41, 1.79)	< 0.0001
Presence of zip code poverty	1.25 (1.10, 1.42)	0.001
Residence in health professional shortage areas	1.01 (0.91, 1.12)	0.921
Residence in worst ranked states for public health infrastructure	1.17 (1.05, 1.30)	0.003
Lack of health insurance	1.46 (1.16, 1.84)	0.002
Residence in a rural area	1.02 (0.74, 1.42)	0.902
Social isolation I*	1.25 (1.00, 1.60)	0.054
Social isolation II**	1.02 (0.88, 1.19)	0.775

*Not seeing friends/family members more than once a month.

**Not having anyone to care for you if you become seriously ill or disabled.

***Abbreviations: HR, Hazard ratio; CI, Confidence Interval.

any adverse social determinants of health, the hazard ratio for having one social determinant of health was 1.26, 95% CI 1.02–1.55; for having two social determinants of health was 1.38, 95% CI, 1.12–1.71; and for having three or more social determinants of health was 1.51, 95% CI, 1.21–1.89 (26). Among participants who were aged ≥75 years, none of the observed effects reached statistical significance (26). These results indicate that specifically targeting individuals with multiple social determinants of health may help lower risk of stroke among disparate populations.

To explore the concepts of location of residence, chronic psychosocial stress, and stroke outcomes by race, we assessed the relationship between nineteenth century U.S. census data (1860) and twenty-first century U.S. Centers for Disease Control data (2011–2013) (27). We found that stroke deaths in the twenty-first century were higher in nineteenth century slave counties versus non-slave counties, driven by significantly higher stroke deaths among Blacks still residing in those primarily Southern slave counties (27). Specifically, county-level slavery was related to higher all-race stroke mortality versus non-slave counties (mean difference was 15.0, 95% CI, 14.1–16.0). Among non-Hispanic Whites, stroke deaths in previous slave counties were higher than in previous non-slave counties (mean difference was 12.5, 95% CI,

10.5–12.4, $p < 0.001$) (27). Among Blacks, stroke deaths in previous slave counties were higher than in previous non-slave counties (mean difference was 31.8, 95% CI, 28.4–35.4, $p < 0.001$). Among Hispanics, stroke deaths in previous slave counties were just slightly lower than in previous non-slave counties (mean difference, –3.4, 95% CI, –6.5 to –0.3, $p < 0.001$). Interestingly, we also noted a dose response association of previous slave density on contemporary stroke mortality, such that among 1,134 counties with a history of slavery, stratified by race, a 1% rise in slave density was associated with a 0.07% decrease (per 100,000) in White race stroke mortality (incidence rate ratio of 0.9993, 95% CI, 0.9990–0.9996, $p < 0.001$) but a 0.82% increase (per 100,000) in Black race stroke mortality (incidence rate ratio of 1.0082, 95% CI, 1.0080–1.0085, $p < 0.001$) (27). In another study, we evaluated the association between the discriminatory housing policy of "redlining" (1934–1968) and contemporary stroke prevalence rates in New York City (2014–2018) (28). After adjusting for several confounders including socioeconomic variables, historical redlining was independently linked to higher community-level stroke prevalence (odds ratio of 1.02, 95% CI, 1.02–1.05) (28).

Color Code

It is typical for researchers to pinpoint health disparities using self-reported race or ethnicity, which is a gauge of individuals' social and cultural affiliations. However, racial/ethnic self-identifications can be influenced by the nature of survey queries and can evolve over time, thereby resulting in misleading interpretations about trends in health disparities (29). To add more context to the issue of self-identified race/ethnicity, the approach of also evaluating health disparities using interviewer-ascribed skin color (i.e., "colorism") is gaining traction in certain quarters (29). Moreover, perceived skin color can potentially affect an individual's proximity to socioeconomic resources and can occur both between races/ethnicities and within races/ethnicities (29). It is thought that skin color may provide a phenotypical indicator of a lifetime exposure to racial discrimination encountered within U.S. social systems, thus capturing an understudied relationship between an obscure form of psychosocial stress and health outcomes, which goes beyond the customary links between discrimination or socioeconomic status and health status. Several studies have shown links between interviewer-ascribed or self-reported skin color and stress-related health conditions such as hypertension and depression (29-36). Among individuals of African ancestry, those who are darker skinned tend to

have higher average blood pressures than those who are lighter skinned (30-32). Two major competing explanations have been proposed for the higher prevalence of hypertension in darker-skinned Black individuals: a genetic hypothesis and a sociocultural hypothesis (29-31). With the genetic hypothesis, it is thought that dark skin color, as an indicator of African ancestry, is related to a genetic predisposition for hypertension. With the sociocultural hypothesis, it is thought that dark skin color, as an indicator of lower-ranking social status within a society, subjects dark-skinned individuals to more discrimination and fewer opportunities/resources, which may raise the likelihood of hypertension (29-36). Testing the sociocultural hypothesis would require the assumption of a shared cultural model, which allocates a meaning to skin color variation, and an avenue to define the color status of any given individual per that model (29). Brazil is one of the few countries in which the relationship between skin color and health status is routinely studied and results published. Interestingly, data on stroke mortality for the year 2010 collected by the Mortality Information System of the Brazilian Ministry of Health showed progressively higher (and significantly greater) mortality rates for hypertension, ischemic stroke, and intracerebral hemorrhage, going from "White" Brazilians to "Brown" Brazilians to "Black" Brazilians (37). Future studies will need to utilize appropriate conceptual models to evaluate the association of skin color with stroke risk and consider focusing such analyses on early adulthood, a period in which the psychosocial stress linked to race and ethnicity has just started to accrue.

Epigenetic Code

Unlike the genome, the epigenome can be modified (38). Epigenetics refers to differences in gene expression, minus DNA sequence variation, resulting in varying phenotypes (i.e., inheritance over multiple generations through epigenetic marks but not in an evolutionary way) (38). Epigenetic mechanisms include DNA methylation, which can change over an individual's lifetime, and have been shown to regulate the biological processes underlying atherosclerosis, inflammation, hypertension, and diabetes (38). Gene expression can be altered by the environment; when an environmental stressor is removed, the epigenetic mark fades, and DNA can gradually revert to original programming. Certain dietary and exercise profiles have been linked with unfavorable epigenetic modification (e.g., folate deficiency). Pharmacological agents can affect epigenetic mechanisms to reprogram cells and

tissues with aberrant gene expression and function associated with various disease states (38).

Epigenetics may help us better understand and overcome health disparities (39). First, African Americans are exposed to higher levels of ambient air pollution than Whites, as they are more likely to be of low socioeconomic status and reside in dense urban areas. Greater exposure to air pollution is associated with DNA methylation changes (39). Second, African Americans endure more psychosocial stress than non-Hispanic Whites due to lower socioeconomic status and discrimination. Psychosocial stress has been linked to DNA methylation (39). Third, although African Americans typically have worse smoking-related disease outcomes, studies have shown that smoking causes alterations in DNA methylation patterns (39).

Genetic heritability explains less than 40% of stroke risk with high monozygotic twin concordance (40,41). While African Americans are more likely to experience strokes versus other racial groups, there is limited information about the role of epigenetic pathways in this heightened risk. Evaluation of epigenetic-related mechanisms may provide insight into how environmental and lifestyle factors, which disproportionately affect racial and ethnic minorities, can cause aberrant gene expression patterns over a lifetime, resulting in higher stroke risk (41-43). DNA methylation is an important epigenetic mechanism in the occurrence of stroke. DNA methyltransferases aid the transfer of methyl groups from S-adenosylmethionine to specific cytosine residues located across various genomic regions, which ultimately results in the repression of transcription (41-43). The activity of methyltransferases is influenced by several factors such as age, sex, race, lifestyle choices, and folate status (41-43). Of note, these factors that influence differential DNA methylation at CpG (areas of DNA where a cytosine nucleotide is accompanied by a guanine nucleotide in the linear sequence of bases along its $5' \rightarrow 3'$ direction) sites are also risk factors for stroke (41-43). So far, epigenetic therapeutic approaches for stroke have focused on post-ischemic injury and recovery and not necessarily on stroke risk or racial disparities in stroke risk (41). While agents such as hydralazine inhibit DNA methyltransferase directly or by reducing its gene expression, no epigenetic drugs for cardiovascular disease risk have so far been approved by the U.S. Food and Drug Administration (41-43).

We recently conducted a scoping review of studies published in PubMed between July 1993 and July 2003 on epigenetics and stroke/stroke risk factors and then summarized the results, including

distinguishing the results for people of African descent (44). Of 104 studies, only six studies specifically looked at epigenetic mechanisms and stroke risk in people of African ancestry. Results of these studies show that patterns of DNA methylation and long non-coding RNA influenced by lifestyle, environmental exposures, and Factor VIII levels raise stroke risk in people of African ancestry (44). However, none of the studies specifically evaluated epigenetic patterns as actionable targets for reducing the influence of psychosocial stressors and excess stroke risk in people of African ancestry (versus other racial and ethnic groups) (44). Also, none of the studies assessed the role of established or novel therapeutic cardiovascular agents with the potential to reprogram DNA by adding or removing epigenetic markers in people of African ancestry (44). As a public health priority, it will be important to include individuals from underrepresented communities who tend to experience the greatest burdens of stroke in environmental epigenomics research as a potentially expedient way to better understand the upstream determinants of these long-standing unequal cerebrovascular disease burdens (43).

CONCLUSIONS

In the last fifty years, the disproportionately higher burden of stroke risk experienced by people of African ancestry in the United States, compared to their non-Hispanic White counterparts, has not been alleviated. If anything, signs point to the disparity potentially worsening in the years to come. On one hand, we can explain about half the excess stroke risk seen among African Americans, which is due to a higher prevalence of conventional risk factors. Certainly, much more concerted effort needs to be applied to controlling these traditional risk factors through sustained patient/provider education, trust building, and community partnerships (45). On the other hand, we need more granular understanding of the contributors to the unexplained excess stroke risk seen in African Americans. Fortunately, there are several promising avenues to explore to further decode stroke disparities (Table 4). Prominent among them are the social determinants of health including psychosocial stressors related to zip codes and color codes, as well biological mechanisms related to epigenetic codes (46). Tackling the toll of stroke on vulnerable and underserved communities within United States will require bold and decisive action from several major stakeholders (46). The ideal future research template to eliminate stroke disparities research will require interventions

TABLE 4
Potential Overarching and Specific Questions to Be Addressed in Future Stroke Disparities Research

Overarching Questions	❑ What are the joint and distinctive impacts of psychosocial stress on epigenetic markers (e.g., DNA methylation changes)? ❑ Is the excess stroke risk seen among African Americans explained by differences in unique modifiable epigenetic patterns caused by psychosocial stressors? ❑ Are these epigenetic markers potential targets for novel or established therapeutic agents?
Specific Questions	❑ Among individuals in late adolescence and early adulthood, what are the epigenetic markers linked to ascribed darker skin color in Western societies? ❑ Among individuals in late adolescence and early adulthood, what are the epigenetic markers linked to lived experience in racially segregated Black neighborhoods? ❑ Among individuals in late adolescence and early adulthood, what are the epigenetic markers linked to uniquely deleterious health behaviors in African Americans? ❑ What are the epigenetic markers linked to accumulation of individual- and neighborhood-level exposure to neighborhood industrial air pollution? ❑ What are the epigenetic markers linked to accumulation of individual- and neighborhood-level exposure to economic disadvantage? ❑ What are the epigenetic markers linked to accumulation of individual- and neighborhood-level exposure to neighborhood industrial air pollution and economic disadvantage together? ❑ What are the epigenetic markers linked to historical slave colonies and redlining districts? ❑ What are the epigenetic markers linked to high allostatic load, high discrimination scale scores, and serum levels of hormones and cytokines (e.g., resistin, IL6, leptin, and cortisol)? ❑ Which epigenetic markers are differentially and uniquely linked to stroke risk (major risk factors, risk scores, stroke occurrence) in African Americans?

targeting multilevel factors, comprising the individual patient, social supports, provider, practice setting, research milieu, and community environment (47).

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DISCUSSION

Zeidel, Boston: This relates to both of the prior two talks, which were also superb. There was an interesting piece in the Washington Post relatively recently that compared Ashtabula County in Ohio with Erie County in Pennsylvania and Chautauqua County in New York. These counties are adjacent to each other and right on Lake Erie, but they're all in different states. The population demographically is somewhat similar in all three, but the health outcomes in the Ohio county are materially worse. The article described how the mortician there is burying many of his friends at a young age. These are all White folks, but I think this scenario strongly supports what you're saying: it's about the stressors and the fact that the interventions are not being done at the state level to help out. Can you comment on that because I think it's a very interesting natural experiment that's going on?

Ovbiagele, San Francisco: Absolutely! I completely agree. I spoke specifically about racial disparity, but the broader notion is that several types of health disparities, including geographic disparities, are primarily influenced by wider social influences in society, which are probably best addressed through enduring government policies. Not enough has been done to test the effects of policy-level interventions on individuals exposed to higher levels of sustained psychosocial stress due to their race, ethnicity, geography, socioeconomic status, or environment. While I hadn't heard about the situation you mentioned, we need to do much more in that regard.

Zeidel, Boston: Yes, thank you.

T. Maddox, St. Louis: Thanks for the talk. I was intrigued by the potential for contribution of both genetics and environmental stress to the higher stroke rates among people with African ancestry. To tease apart these two potential factors, you could compare the rates between African Americans and native African populations. I imagine African Americans have higher environmental stress rates.

Ovbiagele, San Francisco: Yes, it's a great question and something that I do actually quite a bit in my research. We have several studies of stroke going on, but we are also doing cross-continental comparisons of stroke risk factors among indigenous Africans versus African Americans. While we have not yet done any genetic or epigenetic cross-continental comparisons between these groups, we just completed the first-ever GWAS of stroke among indigenous Africans so those results will be coming out very soon. However, in previous studies, we found that compared to European Americans, the prevalence of hypertension, diabetes, and obesity is much higher among African Americans and indigenous Africans. There is likely a common underlying basis in both these latter groups—whether it is genetic, environmental, or epigenetic—where they are more likely to experience these very common stroke risk factors earlier in life. But what exactly is it? Is it psychosocial stress due to lingering effects of colonialism in Africa or slavery in the United Sates? Is it psychosocial stress due to current effects of tribalism in Africa or racism in the United States? Is it due to the relatively lower socioeconomic status among these groups in both regions? Clearly, there is a lot we need to better understand.

T. Maddox, St. Louis: Thank you.