Commentary: Addressing Racial Disparities in Stroke: The Wide Spectrum Investigation of Stroke Outcome Disparities on Multiple Levels (WISSDOM)

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Racial-ethnic disparities in stroke recovery are well-established in the United States but the underlying causes are not well-understood. The typical assumption that racial-ethnic disparities in stroke recovery are explained by health care access inequities may be simplistic as access to stroke-related rehabilitation, for example, does not adequately explain the observed disparities. To approach the problem in a more comprehensive fashion, the Wide Spectrum Investigation of Stroke Outcome Disparities on Multiple Levels (WISSDOM) was developed to bring together scientists from Regenerative Medicine, Neurology, Rehabilitation, and Nursing to examine disparities in stroke "recovery." As a result, three related projects (basic science, clinical science and population science) were designed utilizing animal modeling, mapping of brain connections, and community-based interventions. In this article we describe: 1) the goals and objectives of the individual projects; and 2) how these projects could provide critical evidence to explain why racial-ethnic minorities traditionally experience recovery trajectories that are worse than Whites. *Ethn Dis.* 2018;28(1):61-68; doi:10.18865/ed.28.1.61.

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Introduction

Disparities in Stroke Recovery

Stroke is the leading cause of severe disability in the United States.[1] Estimates indicate that approximately 795,000 Americans experience a stroke annually.[1] Significant racial disparities exist in stroke recovery among African Americans (AAs) who are at the highest risk for stroke.[2] The impact of higher stroke rates among AAs is compounded by onset of stroke at an earlier age and greater likelihood of death than their White counterparts.[3] Additionally, AAs experience more severe strokes and are less likely to achieve stroke recovery equivalent to Whites.[3] While differences in the duration and severity of risk factors, especially hypertension, are believed to explain much of the stroke incidence, it is not entirely clear why stroke recovery would be worse among AAs.

Residence and Stroke

Compounding issues related to race/ethnicity is where one lives (resi-

dence), which also appears to be a contributor to poor stroke recovery. The incidence and prevalence of stroke is higher in the "stroke belt"; a group of states primarily in the southeastern United States.[4] Recent research has also identified a "diabetes belt" that covers the same region where diabetes rates are 3.5% higher than the rest

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of the nation.[5] Further, AAs in the southeastern US represent a larger proportion of the regional population than other northern and western US regions.[6] The extent to which these collective factors impact stroke recovery is not well-understood.

Location of WISSDOM Center

Charleston, South Carolina (SC) serves as home to the WISSDOM Center; the city is in the "low country" or low-lying coastal plain of

South Carolina. The low-country area has the distinction of being part of the "stroke buckle" of the "stroke belt," where stroke mortality rates are the absolute highest in the United States.[4]

Previous Research Related to WISSDOM Focus

Prior work related to stroke in SC has shown that acute stroke outcomes are worse among AAs when compared with Whites across all age groups.[7] Similarly, state-level data have shown that risk of recurrent stroke, myocardial infarction, and death was higher in AAs than Whites.[8] In addition, studies of age and race trends in stroke hospitalizations in SC indicate that, while stroke hospitalization rates decreased over time for both AAs and Whites aged >65 years, for those aged >65 years, there was a 17.3% stroke hospitalization increase among AAs yet no increase among Whites. These findings indicate a racial disparity despite dramatic gains nationwide in stroke reduction.[9] Finally, a study of 162 stroke survivors revealed that AAs were less likely to report independence in overall functional performance at one year when compared with Whites, even after controlling for stroke severity.[10] Collectively, these findings provide strong evidence of racial differences in stroke recovery in South Carolina.

WISSDOM Focus – Stroke Recovery

WISSDOM investigators serve a population that is at elevated risk for stroke and frequently lives in rural "stroke buckle" areas with less than optimal access to care. Therefore, the primary focus of WISSDOM is to better understand racial-ethnic disparities in stroke recovery in the region. As we see it, recovery, or lack thereof, after stroke is a lifelong process. Recovery itself implies a journey back toward a prior state or recapturing properties or abilities that the individual once possessed before stroke. For some individuals, recovery means restoration of all prior function before stroke and anything less is suboptimal. For others, probably the majority, recovery means a (hopefully smooth) transition to a new set of realities post-stroke.

Funding Mechanism

WISSDOM was funded under the American Heart Association (AHA) Strategically Focused Disparities in Cardiovascular Disease Research Network Award in 2015. The AHA created the Strategically Focused Research Network (SFRN) to address key strategic issues.[11] The focus of the current SFRN is cardiovascular disease and stroke.

WISSDOM SUPPORTING CONCEPTUAL FRAMEWORKS

The current literature offers many frameworks that support the conceptualization of the WISSDOM goals and objectives related to translational health disparities
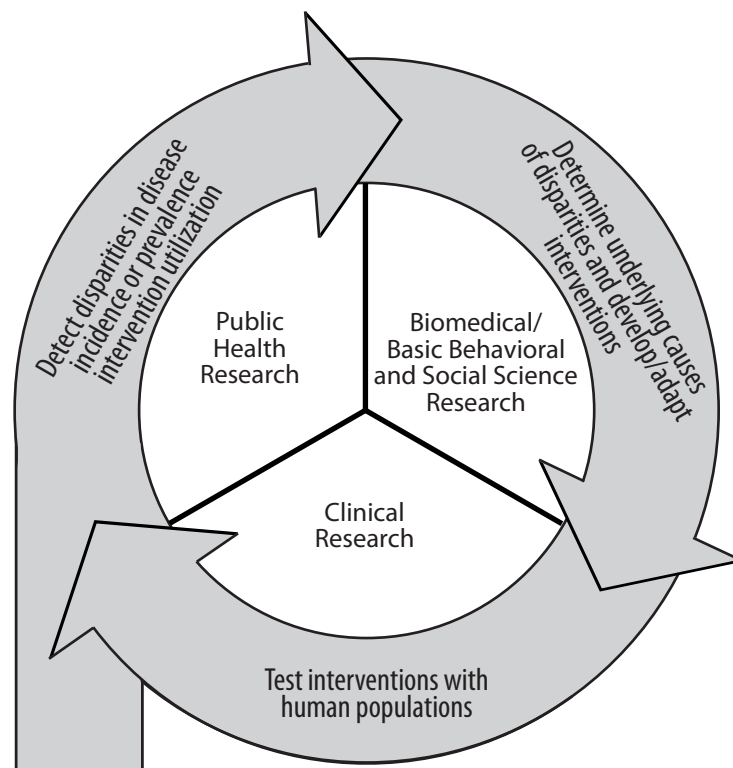

Figure 1. Health disparities research framework, proposed by Fleming and colleagues[12]
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stroke research. WISSDOM investigators selected two frameworks to drive the research focus and expected outcomes. The first framework was proposed by Fleming and colleagues and was designed to illustrate the continuous interdisciplinary focused research collaboration that is required to successfully reduce health disparities (Figure 1).[12] The proposed model emphasizes sequential "translational research" approaches designed to: 1) detect disparities;

2) examine the causes of disparities and develop the necessary intervention to reduce the particular disparity so detected; and 3) implement interventions and monitor outcomes specific to those disparities.[12]

The second framework, the Social Ecological Model (SEM), was selected to highlight the multi-level WISSDOM research philosophy.[13] The SEM emphasizes the multiple influences on health-related outcomes including the individual, peer, com-

munity, institution, and policies. The SEM offers the structure to explore the linkage between the broader external environment (including community and health care systems) and individual and their interpersonal relationships (Figure 2).[14] The model also includes sociodemographic moderators (race/ethnicity, age, income, education, urban-rural residence), psychosocial moderators (self-efficacy, fatalism, perceived social support, interpersonal-family relationships),
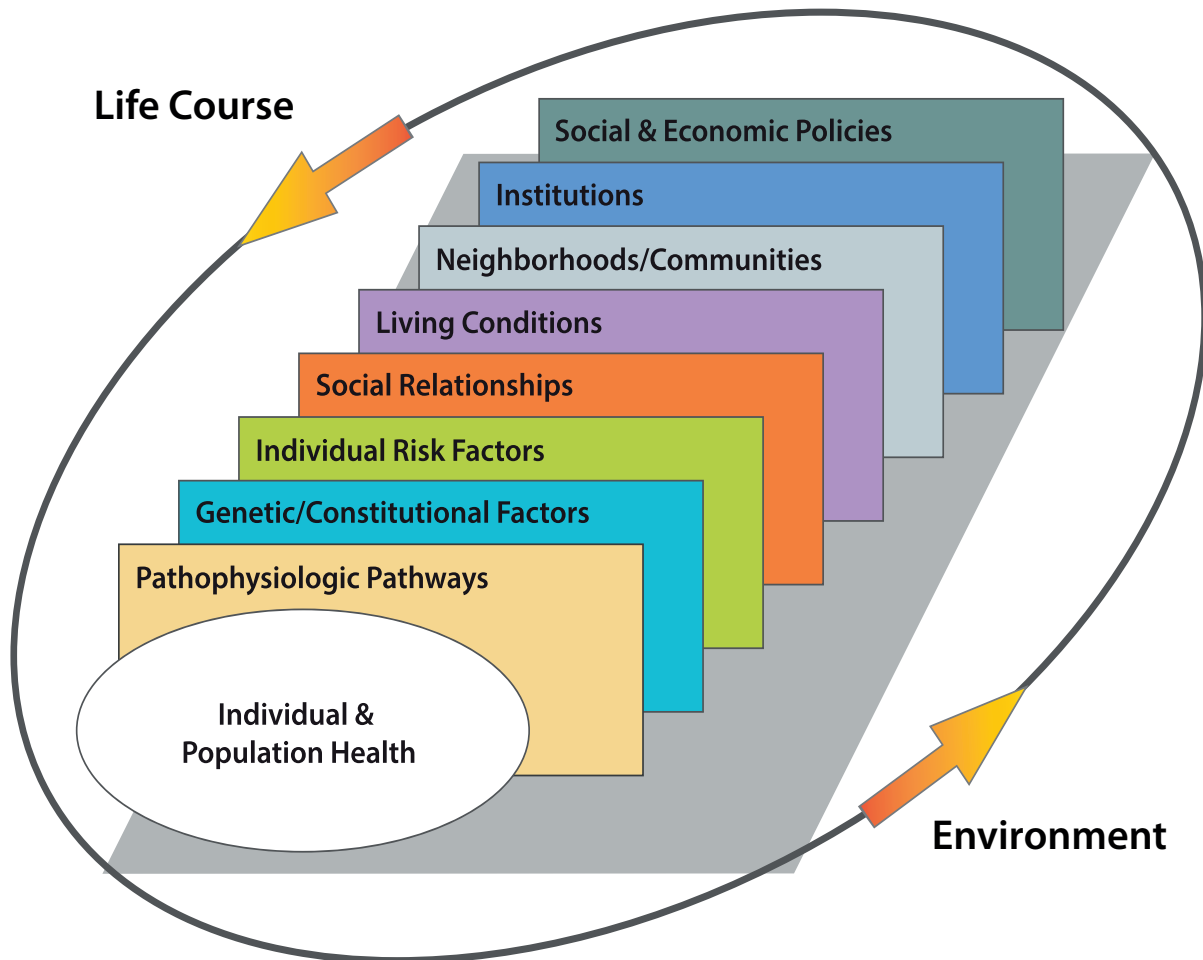

Figure 2. Social ecological model[14]
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Host – Host features (beyond age) that may affect recovery include co-morbidities, arterial stiffness, physical and mental "fitness" prior to stroke and biological factors such as brain-derived neurotrophic factor polymorphism and richness of structural connectome ("plasticity potential"). Both Basic Science project (multi risk factor rat model, middle cerebral artery occlusion as probe with size of infarct and behavioral recovery as outcomes) and Clinical Science project (evaluating the influence of the connectome in motor recovery), operate in this domain.

Acute Treatment – Research completed by WISSDOM investigators have shown no systematic differences in acute treatment along the race-ethnicity axis.

Lesion Post Treatment –The lesion after treatment will not be the prime focus but instead Cortical Spinal Tract damage mapping will be used to select subjects with comparable lesions at least with respect to motor function.

Early Rehabilitation – Control of rehabilitation is not feasible for this project (In the sense of paying for inpatient rehabilitation for uninsured people) but the rehabilitation will be characterized and included as a covariate.

The Outcome Long Term – The Population Science Project will use community engaged research approaches to collaboratively: (a) identify likely contributors to post-stroke recovery deficits in African Americans at the patient, family, and community levels; (b) use this information to develop a community based intervention to address these risk factors; and (c) conduct a pilot RCT of this intervention compared to best practices standard of care.

Figure 3. Recovery from stroke: the conceptual domains.

and clinical moderators (comorbidities). Collectively, these two models provide the necessary focus for WISSDOM research projects, all of which are designed to ultimately improve stroke recovery for all.

WISSDOM Projects

WISSDOM is organized around three research projects and a training center. WISSDOM projects were designed to target post-hospital factors that affect the all-important "last mile" in the stroke recovery experience (Figure 3).

Project #1 (Basic Science) - Metabolic Determinants of Vascular Stiffness in Health Disparities Stroke

The objective of this basic science project is to evaluate the impact of "host" factors on stroke recovery using a novel animal approach. The project was designed to model recovery from middle cerebral artery (MCA) occlusion in obese rats and compare those observations to lean rats. Basic science studies have traditionally focused on the role of cerebral ischemia and reperfusion injury in young animals of a pristine background. This study is designed to explore the mechanisms associated with stroke in animals and translate those to humans. Thus, this study will evalu-

ate a rat model of cerebral ischemia to determine the impact of obesity, diabetes, age, salt sensitivity hyperlipidemia, and hypertension on inflammation and reactive oxygen species (ROS) during stroke recovery.

Hypotheses for this study include: 1) In animal models with heavy negative vascular risk, MCA occlusion is associated with an increase in inflammation that results in cell death and decreased functional recovery compared with low burden animals who receive the same induced lesion; 2) In animal models with heavy negative vascular risk, MCA occlusion is associated with an increase in lysosomal membrane permeability, and release of cathepsin B, that result in more ischemic injury and less functional recovery compared to low burden animals; and 3) Inhibition or loss of cathepsin B activity leads to a reduction in apoptosis, ROS, inflammasome activation resulting in relative vascular protection and enhanced recovery compared with animals without this intervention.

To test hypothesis 1, Zucker fatty and lean rats and stroke-prone spontaneously hypertensive (SHRSP) rats will be used to determine the changes in inflammation and other markers of stroke risk in the brain following cerebral ischemia and reperfusion injury. For hypothesis 2, Zucker fatty and lean rats and SHRSP rats will be used to determine the impact of stroke risk factors on stroke recovery. For hypothesis 3, experiments will be designed to determine the impact of cathepsin B on inflammatory mechanisms associated with

stroke. Rats and mice will be given a stroke and then treated with inhibitors at various timepoints to determine the impact of inflammation and inflammasome markers.

It is expected that this project will offer mechanistic information on "if" and "how" a higher burden of negative vascular health factors (obesity, diabetes, age, salt sensitivity and hyperlipidemia) influences the induction of ROS production and activation of inflammation known to decrease stroke recovery. Specifically, information on how

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WISSDOM projects were designed to target post-hospital factors that affect the all-important "last mile" in the stroke recovery experience.

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the burden (low vs high) of factors contribute to vascular health will be utilized to design therapeutic approaches to treat stroke in humans.

Project #2 (Clinical Science) - Influence of Pre-morbid Brain Health on Stroke Recovery

The objective of this clinical science project is to evaluate the relationship between cardiovascular risk factors, degrees of physical and mental activity prior to the stroke, brain tissue integrity, and neurological recovery after the stroke. The study will utilize neuroimaging techniques to

assess the architecture of neural connectivity in the brain connectome. The brain connectome is an individualized and comprehensive map of structural connectivity in the brain, which provides a signature measure of brain network arrangement and complexity. The specific aims of this project are: 1) To stratify brain connectome attributes in a cross-sectional mixed-race sample of stroke survivors in relation to cardiovascular risk factors and degrees of physical and cognitive activities prior to the stroke; and 2) To assess the relationship between richness and integrity of the connectome and stroke recovery.

For Aim 1, data will be collected to evaluate the relationship between pre-stroke cardiovascular risk factors (arterial stiffness, genetic polymorphisms of the Brain Derived Neurotrophic Factor), pre-morbid reading abilities, exercise habits, and connectome network properties of the contralateral brain hemisphere of patients using a surrogate measure of pre-stroke brain health. For Aim 2, short- and medium-term stroke recovery data and quantitative measures of organized brain networks obtained from the connectome will be evaluated in relationship to stroke recovery.

It is expected that a better understanding of the individualized and comprehensive map of the brain connectome will provide the team an individual measure of brain complexity for each stroke survivor. This information will provide information about brain organization before and after stroke and which factors are related to a protective advantage for stroke recovery.

Project #3 (Population Science) - Community-based Intervention under Nurse Guidance after Stroke (CINGS)

The objective of this population science research is to explore the contributors of worse recovery among AAs relative to Whites. To date, it is unclear why racial-ethnic disparities in stroke recovery exist and consequently treatments designed to improve stroke recovery in AAs have been slow to emerge. It is tenable that patient-related factors (expectations and confidence in their recovery) contribute to the racial disparity gap that currently exists. In addition, it is possible that the families of stroke survivors and the communities where they reside also contribute to the disparities in stroke. Therefore, interventions designed to improve stroke-related outcomes in AAs must also consider family and community factors during the development and implementation of novel interventions.[15]

The specific aims of this project will be achieved in three phases:

Phase 1: Formative Identification of Intervention Targets with Major Community Input (Qualitative)

Aim 1. To document the perceived barriers and facilitators of post-stroke recovery (functional, psychosocial status and quality of life) in AAs with stroke, their families, community leaders, health providers, and rehabilitation specialists.

Phase 2: Intervention Development and Pre-Testing

Aim 2. To develop the CINGS intervention components to improve: a) stroke recovery; b) blood pressure control; and c) community participation in stroke recovery activities by integrating evidence-based guidelines and community-generated evidence to address factors that perpetuate disparity in stroke recovery.

Aim 3. To refine the CINGS intervention via: a) a review by experts; b) focus groups of AAs with stroke; c) health provider focus groups; and d) finalizing the intervention.

Phase 3 Pilot-Testing to Obtain Estimates of Variability and Preliminary Evidence of Impact

Aim 4. The developed intervention will be field-tested utilizing randomized control trial and Reach Effectiveness Adoption Implementation Maintenance (RE-AIM)[16] framework to evaluate the intervention.

In Phase 1, the project is designed to identify the factors that contribute to racial differences in stroke recovery. Traditionally, scientists have primarily targeted the patient themselves. The project takes a multi-level approach to explore participant/patient, families and community. In Phase 2, information obtained in Phase 1 will be used to develop an intervention delivered by nurses and community health workers to improve recovery after stroke. The intervention will be tested in Phase 3 of the project.

It is expected that by addressing stroke recovery not only at the level of patient, but also at family and community levels, critical factors related to poor stroke recovery in AAs will be identified and integrated into novel interventions. More specifi-cally, it is anticipated that this novel research project will help the team: a) understand how patient, family, and community level factors contribute to stroke recovery; b) engage community members (stroke survivors, health providers, families) particularly racial minorities who will be critical to the development of targeted interventions necessary to close the racial disparity gap in stroke recovery; and c) integrate knowledge obtained from the project to address the critical interplay of socio-environmental and behavioral factors necessary for the development of multi-level community based interventions for community dwelling AAs with stroke. The outcomes of this project will build on the growing literature related to environmentally guided lifestyle and self-management programs.[17,18]

WISSDOM TRAINING PROGRAM

The primary goal of the WISSDOM training program is to develop new investigators who will advance stroke recovery research. The training program is organized to facilitate a synergistic partnership between mentors and mentees with a specific focus on stroke recovery and the challenges associated with poor recovery among AAs. It is expected that the training program will develop properly trained junior investigators who will lead future biomedical stroke research. Both the WISSDOM training and research projects are supported by an advisory committee.

The training program will be systematically incorporated into the

three WISSDOM research projects. The specific aims of the WISSDOM training program are: 1) To select qualified scientists with potential to contribute to current and future knowledge in stroke outcomes and disparities research; 2) To increase fellows' knowledge, skills, and motivation to develop independent research careers in stroke recovery and disparities research; 3) To provide fellows with intensive individualized training and guidance in grant writing; and 4) To empower fellows to become independent scientists by maximizing their career development opportunities using a congruent mentoring model.

This training program will establish a network of junior faculty with varied research expertise in the areas of stroke recovery and disparities research.

Conclusions

WISSDOM research projects are designed to examine racial-ethnic disparities in stroke recovery in innovative ways by using a comprehensive approach (basic, clinical, and population science research). These research efforts will inform one another and facilitate the development of novel interventions to both improve stroke recovery and reduce the racial disparity that currently exists. Finally, the WISSDOM training center will address the lack of scientists trained in translational stroke research.

This paper describes the development of a research center. All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent will be obtained from all individual participants included in future studies.

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Adams, Magwood, Kindy, Bonilha, Lackland; Acquisition of data: Adams, Magwood, Kindy, Bonilha; Data analysis and interpretation: Adams, Magwood; Manuscript draft: Adams, Ellis, Magwood, Kindy, Lackland; Statistical expertise: Lackland; Acquisition of funding: Adams, Ellis, Magwood, Kindy, Bonilha; Administrative: Magwood, Kindy, Lackland; Supervision: Magwood, Kindy, Bonilha

References

1. Horner RD, Matchar DB, Divine GW, Feussner JR. Racial variations in ischemic stroke-related physical and functional impairments. *Stroke*. 1991;22(12):1497-1501. https://doi.org/10.1161/01.STR.22.12.1497. PMID:1962323.
2. Cruz-Flores S, Rabinstein A, Biller J, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council on Quality of Care and Outcomes Research. Racial-ethnic disparities in stroke care: the American experience: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(7):2091-2116. https://doi.org/10.1161/STR.0b013e3182213e24. PMID:21617147.
3. Burke JF, Freedman VA, Lisabeth LD, Brown DL, Haggins A, Skolarus LE. Racial differences in disability after stroke: results from a nationwide study. *Neurology*. 2014;83(5):390-397. https://doi.org/10.1212/WNL.0000000000000640. PMID:24975857.
4. Liao Y, Greenlund KJ, Croft JB, Keenan NL, Giles WH. Factors explaining excess stroke prevalence in the US Stroke Belt. *Stroke*. 2009;40(10):3336-3341. https://doi.org/10.1161/STROKEAHA.109.561688. PMID:19679841.
5. Barker LE, Kirtland KA, Gregg EW, Geiss LS, Thompson TJ. Geographic distribution of diagnosed diabetes in the U.S.: a diabetes belt. *Am J Prev Med*. 2011;40(4):434-439. https://doi.org/10.1016/j.amepre.2010.12.019. PMID:21406277.
6. US Census Bureau, Quick Facts, South Carolina 2017. Last accessed December 17, 2017 from https://www.census.gov/quickfacts/fact/table/SC,US/BZA010215.
7. Feng W, Nietert PJ, Adams RJ. Influence of age on racial disparities in stroke admission rates, hospital charges, and outcomes in South Carolina. *Stroke*. 2009;40(9):3096-3101. https://doi.org/10.1161/STROKEAHA.109.554535. PMID:19542054.
8. Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. *Neurology*. 2010;74(7):588-593. https://doi.org/10.1212/WNL.0b013e3181cff776. PMID:20157161.
9. Boan AD, Feng WW, Ovbiagele B, et al. Persistent racial disparity in stroke hospitalization and economic impact in young adults in the buckle of stroke belt. *Stroke*. 2014;45(7):1932-1938. https://doi.org/10.1161/STROKEAHA.114.004853. PMID:24947293.
10. Ellis C, Boan AD, Turan TN, Ozark S, Bachman D, Lackland DT. Racial differences in poststroke rehabilitation utilization and functional outcomes. *Arch Phys Med Rehabil*. 2015;96(1):84-90. https://doi.org/10.1016/j.apmr.2014.08.018. PMID:25223490.
11. Muntner P, Becker RC, Calhoun D, et al. Introduction to the American Heart Association's Hypertension Strategically Focused Research Network. *Hypertension*. 2016;67(4):674-680. https://doi.org/10.1161/HYPERTENSIONAHA.115.06433. PMID:26902490.
12. Fleming ES, Perkins J, Easa D, Conde JG, Baker RS, Southerland WM, et al. 2008. The role of translational research in addressing health disparities: a conceptual framework. *Ethn Dis*. 2008; 18(2 Suppl 2): S2–155-60. Last accessed December 17, 2017 from https://ethndis.org/priorsuparchives/ethn-18-02s2-155.pdf
13. IOM (Institute of Medicine). *Promoting Health: Intervention Strategies from Social and Behavioral Research*. Washington: DC National Academy Press; 2000:43.
14. Kaplan GA, Everson SA, Lynch JW. The contribution of social and behavioral research to an understanding of the distribution of disease: a multilevel approach. In: Smedley BD, Syme SL, eds. *Promoting health: intervention strategies from social and behavioral research*. Washington, DC: National Academies Press; 2000.
15. Blixen C, Perzynski A, Cage J, et al. Stroke recovery and prevention barriers among

young African-American men: potential avenues to reduce health disparities. *Top Stroke Rehabil*. 2014;21(5):432-442. https://doi.org/10.1310/tsr2105-432. PMID:25341388.

16. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. 1999;89(9):1322-1327. https://doi.org/10.2105/AJPH.89.9.1322. PMID:10474547.

17. Kendall E, Foster MM, Ehrlich C, Chaboyer W. Social processes that can facilitate and sustain individual self-management for people with chronic conditions. *Nurs Res Pract*. 2012;2012:282671. https://doi.org/10.1155/2012/282671. PMID:23227321.

18. Wiltsey Stirman S, Kimberly J, Cook N, Calloway A, Castro F, Charns M. The sustainability of new programs and innovations: a review of the empirical literature and recommendations for future research. *Implement Sci*. 2012;7(1):17. https://doi.org/10.1186/1748-5908-7-17. PMID:22417162.