FIU
Robert Stempel College of Public Health & Social Work

UsAgainstAlzheimer's

Priorities for Optimizing Brain Health Interventions Across the Life Course in Socially Disadvantaged Groups

EXECUTIVE SUMMARY

This report underscores the need for non-pharmacological intervention research to reduce risk of Alzheimer's disease and related disorders among individuals from socially disadvantaged groups most at risk for cognitive decline, yet least likely to be included in dementia research. The report addresses this gap by highlighting scientific findings presented at the 2019 symposium at Florida International University, *Presenting Brain Health in Disadvantaged Communities: Exploring Pathways to Intervention Development*. The daylong symposium focused on U.S.-based, cutting-edge dementia research that can inform the next generation of non-pharmacological brain health interventions with implications for populations most at risk for Alzheimer's and related disorders.

Developed by three symposium rapporteurs, the report focuses on the implications derived from 12 expert presentations that addressed genetic, life course, lifestyle, and environmental factors in dementia risk reduction and prevention. The rapporteurs were charged with identifying current research gaps in the optimization of brain health and developing recommendations for action, particularly for at-risk and underrepresented groups such as racial and ethnic minorities.

The report specifically focuses on African Americans and Latinos due to their higher dementia risk status and underrepresentation in basic clinical and translational dementia research. Brain health (also known as cognitive health) is defined as the ability to maintain an active mind and organize one's daily functioning. This is done through making the most of one's ability to remember, learn, plan, concentrate, and control motor, emotional, and sensory function.[1, 2] Although the report highlights Alzheimer's disease, there are associated neurocognitive disorders that can present significant challenges to brain health in socially disadvantaged groups such as frontotemporal dementia, vascular dementia, Lewy body dementia, Parkinson's disease, and Down syndrome, among others.

SUMMARY OF TOPLINE RECOMMENDATIONS

Below are four topline recommendations that emerged as priorities in brain health intervention reasearch.

Advance an intervention research framework that incorporates gene-environment, life course, lifestyle factors, resilience, and chronic disease factors in brain health. This framework should prioritize equity and access goals for communities at higher risk of cognitive decline.

Promote non-pharmacological intervention research that tests different mechanisms of action and at different points of the life course in order to determine whether—and to what degree—cognitive reserve can be maintained and/or brain plasticity can be boosted to reduce dementia risk.

Integrate gene-environment interaction research within non-pharmacologic interventions with both clinical and non-clinical research participants from socially disadvantaged groups at higher dementia risk.

Initiate federal government pilot research projects led by the Centers for Disease Control and Prevention, aimed at attaining a higher state of readiness in chronic disease management programs to promote brain resiliency across state and regional public health agencies.

Introduction

The period between 1990 and 1999 was designated the "decade of the brain" through presidential declaration. This declaration was intended to rally public awareness of the benefits of cutting-edge brain research in the U.S. and research investment.[3] Neurocognitive disorders such as Alzheimer's disease (herein, Alzheimer's) were cited as national research priorities where major strides in the study of genetics, advanced brain imaging, and mapping the brain's biochemical circuitry held promise. In 2011, this mission was advanced when the National Alzheimer's Project Act (NAPA) was signed into law. NAPA established the national goal to prevent and effectively treat Alzheimer's by 2025.[4] This mission could not be more vital today.

Growing Impact

Alzheimer's is the most common progressive neurodegenerative disease, affecting about 50 million people around the world.[5] In 2018, almost 6 million Americans were living with Alzheimer's, a number expected to increase to 14 million by 2050.[6]

The sixth leading cause of death in the U.S., and the only disease in the top 10 causes of mortality for which there is no cure,[7] Alzheimer's is characterized by impaired short-term memory, altered communication, confusion, and behavioral and personality changes. It is one of the most pressing challenges faced by healthcare systems and presents a significant burden on individuals and families, and long-term services and supports,[8] and the U.S. economy.[9]

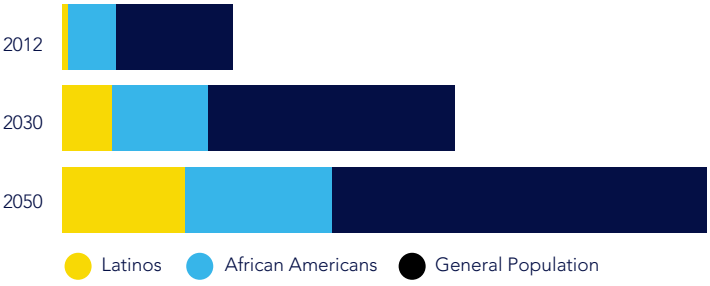
Disparities Impacting Racial and Ethnic Minorities with Heightened Dementia Risk

Alzheimer's and related dementias place particular strain on racial and ethnic minorities due to a number of contributing factors such as aging population growth, dementia risk, and underrepresentation in basic clinical and translational dementia research.

National demographic shifts indicate that the growth of the population age 65 and older is partly fueled by the growth in Latinos[10] and African Americans who are already at increased dementia risk. By 2030, the Latino and African American communities age 65 and older will grow 224% and 114%, respectively, compared to a 65% growth rate for non-Latino white Americans.[11] This trend foreshadows substantial growth in the number of cases of Alzheimer's particularly in underrepresented communities, as the number one risk factor for Alzheimer's is advanced

age.[12] In fact, by 2030, it is projected that the nearly 40% of Americans living with Alzheimer's diseases and related dementias will be Latino or African American.[13]

Americans Living with Alzheimer's



Research underscores that older racial and ethnic groups in the U.S. are particularly challenged with regards to the prevalence and incidence of Alzheimer's.[14,15] Although the biological reasons for this heightened risk are not fully understood, Latinos are 1.5 times more likely to develop Alzheimer's[16] while African Americans are 2 times more likely to develop Alzheimer's compared to non-Hispanic whites.[17] Possible medical factors accounting for this increased risk point to health conditions such as inflammation, hypertension, diabetes, obesity, stroke, and depression, and delayed access to quality clinical diagnostic assessments.[18]

The pronounced underrepresentation of racial and ethnic minorities in Alzheimer's research is a critical concern for the field. For example, it is estimated that racial and ethnic minorities account for less than 5% of Alzheimer's and dementia trials in the U.S.[19] Although federal mandates are intended to ensure the inclusion of diverse research samples, individual, provider, and organizational barriers to research participation continue.[20, 21] Genome-wide association studies (GWAS), based on large clinical samples to ascertain which genes are associated with Alzheimer's, continue to be underrepresentative of diverse U.S. populations.[22]

A Road to Risk Reduction and Prevention

Today, our nation's efforts to address the Alzheimer's crisis have expanded in focus to include the study of non-pharmacological approaches to dementia risk reduction and prevention. By adopting a healthy lifestyle, people can reduce their risk of cognitive decline or dementia. A recent World Health Organization report highlights types of risk-reducing behaviors, including exercise, eating well, managing health conditions (such as diabetes, high blood pressure, and high cholesterol), staying socially engaged, and avoiding smoking, overeating, and excessive drinking. The guidelines suggest that, given changes in these factors, up to one-third of dementia cases may be preventable.[23]

The National Institutes of Health (NIH) is increasingly focused on this pathway with more than 60 non-pharmacological interventions for Alzheimer's under investigation. A four-year NIH-funded study found that lowering systolic blood pressure to a target of 120 mm Hg or lower in people with cardiovascular risk resulted in reducing new cases of mild cognitive impairment (MCI) by 19% and probable dementia by 17%.[24]

The Gap: Identifying Brain Health Interventions for Racial and Ethnic Communities

Despite this promising research, increased focus is needed in rigorously testing and scaling non-pharmacological interventions that hold promise in preventing or delaying cognitive decline in adults due to Alzheimer's and other dementias across the life course. Moreover, special attention must be paid to communities experiencing health disparities at greater dementia risk, including racial and ethnic minorities. Although our nation has invested considerable public resources in cutting-edge ADRD research, underrepresented minorities and socioeconomically disadvantaged adults have lagged behind with respect to the benefits of these scientific advances. Biological, environmental, sociocultural and lifestyle factors play a role in dementia etiology that disproportionately affect older US minorities. For example, under-diagnosis, and low awareness of ADRD, and longer life with cognitive dysfunction is significantly higher in Latinos, limited-English speakers, and persons with low education levels.[25, 26]

An analysis by UsAgainstAlzheimer's of more than 300 peer-reviewed studies focused on non-pharmacological interventions for dementia found that just under 4% focused on racial and ethnic minorities.[27] Overall, just 5% of the studies included a specific or even general strategy for recruiting and retaining underrepresented communities. These gaps deserve urgent attention given the higher risk that these communities face, the growing share of the older adult population they will comprise over the coming decades, and their underrepresentation in Alzheimer's and related dementias research.

A Path Forward

This report addresses the knowledge gap needed to tailor prevention and intervention research across the life course, with particular attention paid to communities at high risk for dementia. The report addresses this knowledge gap by highlighting scientific findings presented at the 2019 symposium at Florida International University, *Presenting Brain Health in Disadvantaged Communities: Exploring Pathways to Intervention Development.*

Presenting Brain Health in Disadvantaged Communities: Exploring Pathways to Intervention Development

Location: Robert Stempel College of Public Health & Social Work, Florida International University, Miami, FL

Monday, June 3, 2019

EXPERT PRESENTATIONS BY THEME

Problem Framing

- Tomás Guilarte, Dean, Robert Stempel College of Public Health and Social Work
- Andrés Gil, Vice President for Research and Economic Development, Dean of the University Graduate School
- Jason Resendez, Executive Director, LatinosAgainstAlzheimer's, UsAgainstAlzheimer's
- William Vega, PhD, Distinguished Professor, Senior Scholar for Community Health, Florida International University

Theme I: Targeting Life Course Factors for Brain Health Interventions

- Peggye Dilworth-Anderson, PhD, Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina, NC
- Yaakov Stern, PhD, Cognitive Neuroscience Division, Department of Neurology, Columbia University, NY

Theme II: Gene - Environment Interaction Mechanisms in Multifactor Interventions

- Jason R. Richardson, PhD, Robert Stempel School of Public Health and Social Work, Florida International University, FL
- Susan M. Resnick, PhD, Laboratory of Behavioral Neuroscience, Intramural Research Program, National Institute on Aging, MD
- Tomas Guillarte, PhD, Department of Environmental Health Sciences, Robert Stempel College of Public Health and Social Work, Florida International University, FL
- Francisco J. Lopera, PhD, Grupo de Neurociencias, Universidad de Antioquia, Colombia

Theme III: Intervention Development and Disentangling the Role of Chronic Disease

- George W. Rebok, PhD, Department of Mental Health, John Hopkins Center on Aging and Health, John Hopkins Bloomberg School of Public Health, MD
- Gladys E. Maestre, MD, PhD, Departments of Neurosciences and Human Genetics, School of Medicine, University of Texas Rio Grande Valley, TX
- April D. Thames, PhD, USC Dana and David Dornsife College of Letters, Arts and Sciences, University of Southern California, CA
- Lisa C. McGuire, PhD, Lead, Alzheimer's Disease and Healthy Aging Program, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention

Although current pharmacological treatments under investigation may provide symptomatic relief and slow the progression of cognitive decline in some people, preventing and delaying the onset of Alzheimer's is one of the most pressing public health challenges of the 21st century. While few brain health interventions exist today that are effective and ready to be scaled for implementation at the community, healthcare system, and community public health levels, this symposium identified interventions at the individual and policy levels that show promise in addressing factors that can prevent or slow progression of the disease.

I. Targeting Life Course Factors for Brain Health Interventions

Reliable evidence shows that greater cognitive reserve is a key biopsychosocial issue in neurodegenerative risk.[28] Higher cognitive reserve protects against clinical symptoms by maintaining superior cognitive functioning, compared to lower cognitive reserve, for people with similar neuropathology. Cognitive reserve refers to physical and functional qualities of the brain such that the physical (passive) quality is attributed to greater brain volume (size) and density, and the functional quality (active) is attributed to greater brain efficiency acquired through formal education, intellectual growth, and relevant social experiences. These are discrete qualities that do not necessarily overlap in the same person. Early life educational attainment, and other brain development activities occurring earlier versus later in the life course, may increase or maintain cognitive reserve by fostering enhanced brain connectivity.[29] [30]

People with higher cognitive reserve may eventually succumb to severe cognitive decline as regions of the brain are progressively affected by Alzheimer's neuropathology. If effective interventions, e.g., cognitive stimulation[31] and behavioral activities,[32] are developed to boost cognitive reserve, it is possible that a higher level of cognitive functioning could be sustained for people with mild cognitive impairment, or even moderate dementia.

Research indicates that some people gain an advantage by reducing the impact of existing neuropathology if they have a natural advantage of being born with larger intracranial volume (larger brains), and/or advantaged by completing more years of formal education.[33] Cognitive reserve has been assessed using educational attainment, vocabulary, and measured intelligence as primary indicators, and secondarily by adult occupational task complexity and social engagement.

Educational attainment is correlated with family socioeconomic status and place of residence, and is not an automatic function of innate intelligence. [34] Lower educational attainment especially low quality school instruction early in life tends to lower lifetime income and access to opportunities across the lifespan to occupational roles that support cognitive reserve. [35]

In summary, lower educational attainment represents both an early life embedded disadvantage and a higher risk of experiencing health-endangering environmental exposures and lifestyles over the life span associated with Alzheimer's.

Recommendations

1. **The Centers for Disease Control and Prevention and the Department of Education should promote pilot research projects** for prevention and treatment of multiple health targets in school settings and test pilot interventions with students and parents, linking child development and health to educational attainment in primary and secondary education in schools serving disadvantaged communities.

2. **Expand non-pharmacological intervention research** that tests different mechanisms of action at different points of the life course in order to determine whether—and to what degree—cognitive reserve can be maintained and/or brain plasticity can be boosted to reduce Alzheimer's risk.

3. **Strengthen support for multi sector research about early childhood education opportunities** with an emphasis on quality, retention standards, and lifelong learning opportunities with adequate support systems. These programs should have adequate linkages to affordable family health and community support programs.

II. Gene - Environment Interaction Mechanisms in Multifactor Interventions

The majority of people living with Alzheimer's are age 65 and older, although the underlying neuropathology can begin up to 20 years previous to onset of symptoms and diagnosis.[36] Marked by progressive cognitive decline and assessed by clinical history, neurocognitive tests, and biomarker-based detection of neuropathic changes, both genetics and socio-biologic environments operate interactively as multiple etiologic factors. This gene-environment interaction approach is important because precision medicine and prevention research will ultimately need to determine how genetic risk factors modulate effects of psychological, social, and noxious environmental factors.

Genetic susceptibility is central to the discussion of Alzheimer's pathology and the search for risk reduction. Genes can be a formidable influence, if not a determinant risk factor for Alzheimer's. For example, the strongest autosomal intergenerational transmission of genes is documented in early onset Alzheimer's, constituting about 5% to 10% of all cases, with determinant genes being APP, PSEN1, and PSEN2.[37] Identification of these genes has been critical in understanding Alzheimer's pathology. For late onset or sporadic Alzheimer's disease, the APOE 4 gene may be a critical factor in 60% to 70% of cases.[38] However, late onset Alzheimer's is caused by multiple factors both genetic and non-genetic. APOE4 and other candidate genes are risk factors for late onset disease, but they are neither determinant (necessary) or essential (sufficient) as a cause of neuropathology of late onset Alzheimer's, and may be less salient in racial and ethnic groups. This is critical as research suggests the protective effects of APOE2 are understudied, and inconsistent associations are reported between Alzheimer's risk and the APOE4 gene among African Americans and Latinos of Caribbean origin.[39]

In 2019, an analysis of genetic data from more than 94,000 individuals revealed five new risk genes for Alzheimer's, many of which are involved with inflammatory processes.[40] Although there are strong genetic influences in late onset Alzheimer's none of these genes alone is sufficient to be causal. This strongly points to the need to determine gene-gene and gene-environment interactions. Some genes may interact with non-genetic factors to increase neuropathology. In other instances, non-genetic factors may reduce the risk of genetic risk factors. A wide variety of genes and non-genetic factors potentially influence neuropathology and, in some cases, can actually present different profiles of neuropathology. For example, Alzheimer's disease biomarkers can differ across groups whereby Latinos and African Americans may have a more inflammatory and vascular Alzheimer's profile than others.[41]

Research to better understand mechanisms by which genetic and non-genetic risk factors contribute to brain pathology in Alzheimer's is essential for designing interventions that have the highest potential to succeed in specific higher risk subgroups. Furthermore, research is needed to recognize individual characteristics that increase or decrease the likelihood that prevention or treatment interventions will be effective. Extant research is not yet sufficiently advanced to support design of a universal intervention model to prevent or slow progression of late onset Alzheimer's disease or other neurocognitive disorders. It is essential to test multiple hypotheses that target different mechanisms of action to determine how best to interrupt the sequence of factors associated with disease onset and progression. This underscores the importance of attentiveness to different responses to intervention approaches in understudied groups such as African Americans and Latinos.

Turning to environmental etiologies for cognitive decline, current evidence suggests that exposure to air pollution, pesticides, and perhaps heavy metals can increase the risk of deficits in cognitive functioning [42, 43] and Alzheimer's.[44, 45] Such exposures are known to be higher in areas of low socioeconomic status and in low-skilled occupations in agricultural and landscaping employment sectors, in which racial and ethnic minorities are overrepresented.

Nevertheless, there are highly accessible population targets for intervention development such as addressing

the toxic effects of pesticides such as DDT and DDE which are significantly associated with higher risk of neuropathology.[46, 47, 48] Thus, modifiable environmental risk factors in terms of toxic exposures to pesticides are prime targets for intervention development, including macro-level policies regarding use, termination, and remediation of such neurological toxins.

Alzheimer's risk for people with complex personal social and disease histories, including time ordered gene-environment interactions, will require careful targeting of risk factors at specific age and disease progression milestones, with longitudinal assessment of intervention outcomes.[49]

Recommendations

1. **Exploratory and confirmatory research** on mechanisms of action involving gene interactions with biopsychosocial factors specific to African Americans and Latinos should be supported in basic clinical and population studies of neuropathology and cognitive functioning.

2. **Gene-environment interaction research** should be integrated within non-pharmacologic interventions with both clinical and non-clinical participants from subgroups at higher risk of Alzheimer's and related dementias.

3. **Prevention research on human exposure to toxic agents** in water, air, heavy metals, pesticides, and other chemical agents should focus on genetic interactions and impact on ADRD in diverse subgroups with differential exposure levels.

4. **Increase the inclusion of racial and ethnic minorities** in genetic, pharmacological, behavioral, and social determinants research related to Alzheimer's disease and related dementias through improved community engagement and collaboration between research centers, social service providers, and minority health providers.

5. **Promote racial, ethnic and genetic diversity** in Alzheimer's research by developing culturally and linguistically attuned best recruitment practices developed in partnership with local community stakeholders.

III. Intervention Development and Disentangling the Role of Chronic Disease

A challenge in developing effective interventions for higher risk populations is engaging them in research and treatment, in part by anticipating barriers such as racial and ethnic discrimination and selecting modifiable factors adjusted to lifestyles, preferences, and pragmatic constraints on participation. Cultural tailoring to avoid rejection of recruitment into research or treatment is a recurring problem given the sensitivity that dementia represents to individuals and families.

How can individual control and self-efficacy be enhanced in order to support optimal brain health? Many African Americans and Latinos experience social conditions associated with poverty, discrimination, chronic stress exposure, anxiety, sleep disorders, metabolic dysregulation, chronic central nervous system activation, and cellular aging. These have quite different personal implications and social meaning for their lives. Health problems can pose a personal threat requiring a psychological response, emotional regulation, and behavioral management. African Americans and Latinos have higher rates of medical conditions such as obesity, diabetes, and cardiovascular diseases, [50, 51] attributable to lifestyle behaviors and environmental conditions that are difficult to modify with any singular intervention. The question remains as to the extent that individual and community risk factors can change in this context.

Evidence exists that cognitive training can improve long-term cognitive functioning in adults with normal cognition.[52] An example is the ACTIVE trial, [53] which tested a cognitive training intervention with non-Latino whites and African Americans (26%). It resulted in improved instrumental activities of daily living and better reasoning and speed abilities. Whether similar results can be obtained with other diverse subgroups is yet unknown.

A critical issue is whether people of different racial, ethnic, social, and educational backgrounds are equally ready to engage in brain training programs that potentially benefit

them. There is experimental evidence that it is possible to attain positive results using learning and problem solving cognitive performance models that focus on both training and engagement with subgroups at higher risk for health disparities and dementia. There is a need to increase enrollment in tailored intervention trials of cognitive performance for higher risk subgroups, and to examine outcome differences by chronic disease status and underlying genetics. This is important because of the high prevalence in middle adulthood of uncontrolled medical conditions such as obesity, diabetes, and cardiovascular disease that produce inflammation and stroke risk, and are putative risk factors for neuropathology. It is critical to reenergize efforts aimed at prevention through adequate exercise, and control of weight, high blood pressure, cholesterol, and inflammation in middle adulthood as the bedrock for promoting brain health in later adulthood before neuropathology begins.

This will require rethinking the culture of health in communities with relevant stakeholders to promote and support more effective stakeholder linkages for awareness and promotion of healthy lifestyles that include brain health. Efforts such as the Bold Infrastructure for Alzheimer's Act and the Healthy Brain Initiative directed by the Centers for Disease Control and Prevention[54] are prime examples of the public health response to Alzheimer's and related dementias.

Recommendations

1. **The Centers for Disease Control and Prevention should empirically evaluate** current state and regional public health agencies' readiness and preparedness to promote brain health in highly impacted communities, and test pilot projects leveraging culturally tailored programs and materials to improve public awareness of brain health through healthy lifestyles, and to support caregivers and dementia-affected families.

2. **The Centers for Disease Control and Prevention should reevaluate current interventions** for prevention and treatment of multiple chronic diseases and inflammation associated with brain resilience, with an aim to redesign and to test pilot projects that improve reach and improved engagement in disadvantaged communities.

3. **Pilot-test multidimensional and multi-target brain heath interventions** based on the best evidence to manage chronic diseases with metrics to determine program reach and outcomes that are of importance to individuals and families, healthcare systems and payers.

Future Directions

While a systematic analysis of brain health interventions was beyond the intent of this report, several genetic, life course, lifestyle, and environmental factors in dementia risk reduction and prevention were presented. In order to identify programs and interventions that hold promise for further research, a multidimensional brain health intervention framework is offered below.

The multidimensional framework is informed by three themes covered during the conference: (1) Life course factors that address brain health interventions; (2) Gene - environment interaction mechanisms in multifactor interventions; and (3) Disentangling the role of chronic disease on brain health outcomes.

This multidimensional framework serves as a tool to assess the promise, relevance, and readiness of non-pharmacological brain health interventions for underrepresented groups.

Multidimensional Brain Health Intervention Framework

1.
Both genetic and environmental factors play a role in Alzheimer's causation and resilience to the disease and its consequences—singularly and in combination (***genetic and environmental factors***).

2.
Observed risk and protective factors have roots in experiences across the life course, including opportunities and social determinants that emerge and interact with one another from pre-conception to advanced age (***life course challenges and opportunities***).[55, 56]

3.
Brain health solutions should optimize multiple life course targets (e.g., educational attainment, diet and nutrition, physical activity, etc.), and identify common pathways of change (***multiple targets and common pathways***).[57]

4.
Disparities in disease burden among underrepresented racial and ethnic minorities, low-income families, and limited-English speakers are exacerbated by low access to quality diagnostic, treatment, and care practices. Thus, interventions should be resourced to support the navigation of culturally and linguistically long-term services and supports (***disparities and social determinants***).[58]

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AUTHORS:

María P. Aranda, PhD, USC Edward R. Roybal Institute on Aging; William A. Vega, PhD, Florida International University; Jason R. Richardson, MS, PhD, DABT, ATS, Associate Dean for Research, Florida International University; Jason Resendez, UsAgainstAlzheimer's.

DISCLAIMER:

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