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Alzheimer's Disease In African Americans: Risk Factors And Challenges For The Future

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Abstract

As the US elderly population continues to expand rapidly, Alzheimer's disease poses a major and increasing public health challenge, and older African Americans may be disproportionately burdened by the disease. Although African Americans were generally under included in previous research studies, new and growing evidence suggests that they may be at increased risk of the disease and that they differ from the non-Hispanic white population in risk factors and disease manifestation. This article offers an overview of the challenges of Alzheimer's disease in African Americans, including diagnosis issues, disparities in risk factors and clinical presentation of disease, and community-based recommendations to enhance research with this population.

Alzheimer's disease continues to be a large and growing public health problem for caregivers and families, health services workers, and policy makers. Occurrence of the disease is strongly related to age, and because the population ages sixty-five and older is growing at a rapid pace, the number of people with dementia is expected to increase significantly in the coming decades. At the same time, the United States is becoming increasingly diverse, particularly among the elderly. In 2010 the US Census Bureau indicated that 20 percent of the US population ages sixty-five and older was a racial or ethnic minority. Current projections suggest that by 2050, 42 percent of the nation's older adults will be members of minority groups. Among those ages eighty-five and older, 33 percent are projected to be a minority.

This demographic shift in both age and racial composition will represent a critical challenge to minority populations, particularly older African Americans, because a growing body of evidence suggests that African Americans may have a greater risk of Alzheimer's disease compared to the non-Hispanic white population. Yet knowledge about diagnosis, mechanisms, management, and treatment of the disease is based almost exclusively on studies of non-Hispanic whites. The lack of high-quality biologic data on large numbers of racial and ethnic minorities poses critical barriers to progress in understanding whether the mechanisms and processes of Alzheimer's disease operate the same or differently in racial and ethnic minorities and, if so, how, particularly in the high-risk African American

population. In this article a brief overview of racial disparities in Alzheimer's is followed by a review of the evidence for disparities in risk factors for clinical manifestations of the disease, recommendations for future directions to expand understanding of Alzheimer's in the African American population, and strategies to guide research efforts in this area.

It is important to note that this review highlights primarily biologic mechanisms underlying health disparities because Alzheimer's disease is a neurodegenerative disease. We do not mean to suggest that biologic differences alone account for disparities in Alzheimer's disease. There is a large and diverse literature on cultural beliefs and perceptions of disease and aging, inequities in health care access, life-course influences, and social and cultural variations in care-giving experiences,^{1,2} and these factors likely intersect with biologic mechanisms in currently unknown ways, resulting in these health disparities for Alzheimer's disease. A comprehensive review of these nonbiologic issues is beyond the scope of this article. However, given the complexity of the disease and the fact that no single factor has accounted for observed disparities, multi-interdisciplinary collaborations that can integrate multidimensional layers of data (such as biologic, social, life course, environmental, and policy) will be necessary to move the field forward and address one of the most urgent public health problems of our time.

Definition Of 'Alzheimer's Disease'

The National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease recently presented a set of revised clinical and pathologic criteria for the disease.³ In the revised criteria, Alzheimer's is recognized as a chronic disease that begins with a pathologic process characterized by deposits of abnormal proteins in the brain in the absence of any detectable cognitive impairment, followed by subtle impairment, and then obvious mild cognitive impairment, with dementia representing only the end stage of the disease.^{3–6} The revised criteria differ from the old criteria by incorporating biomarkers and also by expanding Alzheimer's disease into three phases: an asymptomatic preclinical phase, a symptomatic pre-dementia phase (also known as mild cognitive impairment, or MCI), and a dementia phase. The diagnostic criteria of the asymptomatic phase are intended for research purposes only.

In the crafting of a definition that integrates phases of Alzheimer's disease that precede dementia, the goal is to encourage clinicians toward an earlier diagnosis and treatment. Further, the criteria affirm that Alzheimer's disease is specifically the cognitive impairment that results from a particular set of brain pathologies. However, because many of these brain pathologies are not readily detectable during life, the common usage of the term *Alzheimer's disease* in the literature and in this review refers to the clinical syndrome.

Several facts should be borne in mind. First, in old age, mixed pathologies—for example, the combination of Alzheimer's disease pathology and other common pathologies such as cerebrovascular disease—are the most common cause of the Alzheimer's disease syndrome.⁷ Second, Alzheimer's disease pathology is common in people without overt cognitive impairment.⁸ Third, many risk factors for the clinical Alzheimer's disease syndrome are not directly related to its underlying pathology.⁹ As is discussed in this article,

these facts result in a number of challenges to extrapolating research findings on Alzheimer's disease from studies of predominantly non-Hispanic white populations to minority populations.

Racial Disparities In Alzheimer's Disease

A growing body of evidence suggests that the prevalence of cognitive impairment or Alzheimer's disease may be two to three times higher among older African Americans than in older non-Hispanic whites.¹⁰ Yet results from large population-based studies of the incidence of Alzheimer's disease (that is, new cases of disease) have been mixed.^{11,12} The discrepancy in the literature may stem from the fact that substantial racial disparities exist for cognitive test performance, with older African Americans tending to perform more poorly, on average, than older non-Hispanic whites.¹³ Because level of achievement on cognitive performance tests is still the primary standard for making an Alzheimer's diagnosis, these marked disparities often present unique challenges for diagnosing dementia in older African Americans.

Researchers have used a number of strategies to adjust for poor performance on cognitive tests,¹⁴ but given evidence that African Americans with Alzheimer's disease decline more slowly¹⁵ and have a longer survival rate¹⁶ compared with non-Hispanic whites, it is possible that relying on performance on cognitive tests measured at a single point in time is causing Alzheimer's disease to be overdiagnosed in African Americans. A better strategy, when possible, is to examine change in cognitive function over time. Given that the development of Alzheimer's disease entails a progressive decline in cognitive function, using longitudinal data—where cognition is measured over multiple time points—relieves the challenge of interpreting performance based on a single point in time. Further, the person serves as his or her own control, rather than comparisons with groups that differ on factors that can influence performance (for example, socioeconomic status and health).^{17,18} In fact, studies that compare African Americans to non-Hispanic whites on rates of change over time typically find no or very small differences.¹⁹ Thus, there remain important gaps in the medical literature, and consequently also in understanding of factors that influence Alzheimer's disease among African Americans.

Risk Factors In African Americans

Disease prevention, or delaying disease onset, is likely to be the critical component to reducing racial disparities in Alzheimer's disease. However, disease prevention first requires the identification of risk factors for cognitive decline and dementia, and subsequently the development of strategies to modify behavior or intervene with treatment.

AGE AND GENETICS

The most well-established risk factors for Alzheimer's disease are age and a genetic polymorphism called apolipoprotein E (APOE). Age is strongly linked to risk of disease, with current estimates suggesting a 10 percent increased risk for people older than sixty-five, and a 50 percent increased risk for people older than eighty-five. These rates do not appear to vary by race.

In contrast, the data for APOE have been much more mixed. APOE is a cholesterol transport plasma protein that has three different alleles (e2, e3, and e4) on chromosome 19. The three alleles code for three different APOE isoforms (apoE2, apoE3, and apoE4), which results in six potential genotypes (e2/2, e2/3, e2/4, e3/3, e3/4, and e4/4). An association between the presence of one or more APOE e4 alleles and Alzheimer's disease has been demonstrated in numerous studies.²⁰ There is now fairly good evidence that the APOE e4 allele increases risk of clinical Alzheimer's disease by enhancing the accumulation of Alzheimer's disease pathology: the abnormal brain proteins known as amyloid plaques and neurofibrillary tangles.²¹

The prevalence of the e4 allele is consistently found to be higher in African Americans than non-Hispanic whites,²² but it is inconsistently related to Alzheimer's disease or cognition in this population.¹² However, a recent genome-wide association study (GWAS) using several African American cohorts confirmed that the APOE e4 allele, along with a new gene, ABCA7, is related to an increased risk of Alzheimer's disease among African Americans.²³ The study is noteworthy for two reasons. First, it represents the largest genomewide association study to date involving African Americans—almost all such studies for late-onset Alzheimer's disease have been done with non-Hispanic whites. Second, both genes that were found to be related to an increased risk of Alzheimer's disease are involved in cholesterol transport, and given that cholesterol metabolism has been implicated in Alzheimer's disease,²⁴ this presents a potential target for future intervention studies.

VASCULAR CONDITIONS

Other risk factors for Alzheimer's disease in African Americans are also likely to be related to vascular conditions, although more data are warranted. For example, diabetes has been associated with risk of Alzheimer's disease in many studies of non-Hispanic whites.²⁵ The neurobiologic mechanism linking diabetes to the development of Alzheimer's disease is unknown, but diabetes is a risk factor for clinically diagnosed stroke, particularly subcortical infarcts, and may contribute to cognitive impairment with stroke.²⁶ However, few studies have directly examined the relationship between diabetes and common neuropathologies, and results have been inconclusive.²⁷ Because of the association of diabetes with clinical stroke and vascular dementia, it is plausible that people with diabetes may have more infarct pathology than Alzheimer's disease pathology, but without improved data this cannot be confirmed.²⁸ Regardless, numerous studies have documented a higher burden of diabetes among older African Americans compared to older non-Hispanic whites, including a greater prevalence of risk factors related to diabetes and more diabetes-related complications.²⁹

BODY MASS INDEX

Another potentially relevant risk factor for Alzheimer's disease in African Americans is body mass index (BMI). The relationship between BMI and cognition in old age is complex. Some studies report that low BMI or weight loss is associated with cognitive impairment and dementia, while others have reported an association between high BMI and cognitive impairment, or a nonlinear relationship.³⁰ Few studies have examined racial differences in the association of BMI and dementia. African Americans have a higher prevalence of overweight and obesity compared to non-Hispanic whites and stronger effects of BMI on

various conditions, including diabetes, metabolic syndrome, and hypertension.³¹ Thus, BMI could represent a compelling link with dementia in this population.

OTHER PHYSIOLOGIC RISK FACTORS

Several additional risk factors have also been found to be related to Alzheimer's disease or cognitive impairment in predominantly non-Hispanic white samples, including chronic kidney disease and both lower and higher hemoglobin levels. Because of the well-documented racial differences in many of these conditions and their association with cardiovascular disease, and the fact that cerebrovascular pathology contributes to the Alzheimer's disease syndrome,⁷ studies with large numbers of clinically well-characterized African Americans are needed to determine whether these vascular risk factors increase risk of Alzheimer's disease among African Americans; are related to the neuropathology of Alzheimer's disease in African Americans with and without dementia; or may be modified by social and environmental factors that influence racial disparities in many vascular conditions—such as neighborhood conditions, health care behavior, quality of medical care, and experiences of discrimination in general.¹ In addition, an important implication of a connection between vascular risk factors and Alzheimer's disease is that treatment or elimination of vascular disease in African Americans could have a major impact on Alzheimer's disease diagnoses in this population.

PSYCHOSOCIAL RISK FACTORS

Finally, relatively few studies have examined whether psychosocial risk factors influence risk of disease among African Americans, although many studies have examined these factors in non-Hispanic whites. For instance, there is evidence that living in rural conditions in childhood is related to an increased risk of Alzheimer's disease,³² and one study reported that low levels of education or poor-quality education increased risk of Alzheimer's disease.³³ However, neuroticism, or the tendency to experience psychological distress, was not related to risk of Alzheimer's disease in African Americans, although it was related to the risk of Alzheimer's disease in non-Hispanic whites.³⁴

In contrast to the limited evidence on the relationships between psychosocial factors and incidence of Alzheimer's disease, more studies have examined risk factors for cognitive decline in African Americans. As shown in Exhibit 1, many risk factors for cognitive decline operate the same in African Americans and non-Hispanic whites. For example, results from population- and community-based studies have demonstrated that current smoking and greater depressive symptoms are related to a faster rate of cognitive decline, and the effects do not differ by race. Similarly, both cognitive activity and social networks reduce the rate of cognitive decline—effects that are the same in African Americans and non-Hispanic whites.

In contrast, there are a few risk factors that have been found to operate differently in African Americans and non-Hispanic whites. For example, early-life social adversity or disadvantage was found to be related to a slower rate of decline among African Americans but not non-Hispanic whites, and higher social engagement was related to a slower rate of decline in non-Hispanic whites but not African Americans. Given that cognitive decline is

the hallmark of Alzheimer's disease, these risk factors may provide clues to racial differences in the development of Alzheimer's disease.

Racial Differences In Clinical Manifestation Of Disease

Some studies suggest that the clinical manifestation of Alzheimer's disease may differ for African Americans compared to non-Hispanic whites, in that the former often present with an earlier age of onset and exhibit greater severity of symptoms at the time of presentation.³⁵ This is consistent with the fact that compared to non-Hispanic whites, minorities are less likely to seek medical attention, and when they do, they present later in the disease course.³⁶ It has also been documented that African Americans are less likely than non-Hispanic whites to receive Alzheimer's treatments, such as acetylcholinesterase inhibitors or memantine.³⁷ To what extent these clinical manifestations are due to cultural differences in beliefs about the causes of Alzheimer's disease, mistrust and experiences of discrimination in the health care setting, or culturally determined views on health behaviors and risk perceptions has not been examined, but there is growing awareness that these extrinsic social factors may influence at least some of the disparities in clinical presentation and treatment.^{1,36,38}

Challenges For Future Studies With Older African Americans

Because Alzheimer's disease diagnosis, treatment, management strategies, and prevention studies have focused almost exclusively on the non-Hispanic white population, progress in research on the clinical and neuropathologic characteristics of Alzheimer's in minority groups has been limited. Understanding the biologic pathways linking risk factors to cognitive function is essential for the development of effective preventative therapeutic interventions. It thus is necessary to move toward studies that can address the biologic mechanisms that underlie cognition and identify modifiable risk factors for prevention, including comorbid conditions (for example, vascular disease), social context, health behaviors, and environmental factors in order to significantly advance research on African Americans and Alzheimer's disease.

The recruitment and retention of African Americans in research studies has been challenging, because of cultural and historical barriers, particularly for neurobiologic studies. To improve efforts in this area, recruitment for research must be concentrated on effectively communicating the purpose and intent of research in a way that appreciates the value of the research for the person as well as his or her community. Building on a foundation of shared responsibility and establishing mutually beneficial long-term relationships with the African American community is the single most important strategy for increasing participation in research studies, particularly those that require invasive procedures or clinically oriented data collection. As documented in several studies, networking with gatekeepers of the community (such as leaders of community organizations and pastors) allows researchers to gain insight into the concerns of the community and strategies to engage the community in a way that is mutually beneficial. Similar to community-based participatory research methods, Alzheimer's disease research with African Americans requires a constant presence in the community by researchers who can provide culturally tailored and culturally sensitive educational programs that focus not just

on the specific research studies at hand but, more broadly, on the value of research and the benefits to the community now and in the future.³⁹

It is clear that inclusion of older African Americans, with a wide spectrum of educational and life experiences, in research studies is vital to lessening the impact of the disparities in Alzheimer's risk and disease burden and critical to filling an important gap in knowledge on the transition of healthy aging to dementia in this high-risk population. However, unlike research with the majority population, an understanding of the past abuses experienced by African Americans, particularly as it pertains to research, necessitates additional strategies to keep subjects engaged, including strengthening trust and ensuring transparency, overcoming barriers to participation (such as transportation and caregiving responsibilities), maintaining frequent contact regardless of the funding situation, and disseminating research findings and study updates in a timely and culturally sensitive fashion.

Recommendations For The Future

We recommend four priorities to advance the understanding of Alzheimer's disease in African Americans.

INCLUDE PEOPLE WITHOUT IMPAIRMENTS

First, it is important to increase studies that include African Americans without dementia or cognitive impairment. Most studies to date have been conducted in medical settings with patients who present to a memory clinic with cognitive complaints or have diagnosed disease. Although much has been learned from this approach, risk factors for clinically evident disease may differ from those for risk of disease (that is, in people who do not yet have disease). Further, as discussed earlier, it is well documented that older African Americans tend to present later in the disease process when behavioral symptoms may be more prevalent and cognitive impairment more severe, underscoring the need to recruit and enroll people without dementia.

Given the difficulty in recruiting study subjects for a disease they do not yet have, innovative recruitment strategies must be used, such as partnering with colleagues in social marketing to help advertise for studies, creating culturally inviting brochures that better attract African American participants, and offering services when possible as a means of giving back to the community. For example, if the researcher determines that the population is in need of preventive screening measures, one might partner with departments that can provide free screenings or incorporate mechanisms to give blood reports if participants are asked to donate a blood sample.

BE PRESENT IN COMMUNITIES

The second recommendation is for clinicians and academics to physically go to the communities they serve, instead of waiting for community members to show up at clinics and academic institutions. To attract people without dementia, community-based recruitment strategies must be used. Innovative approaches to overcome barriers that often deter African Americans from participating in research have been found to be useful in many studies. For example, it is important to employ African American team members with extensive ties to

the African American community. In addition, providing culturally sensitive community education or ancillary services, such as health screenings or educational presentations, is often viewed as mutually beneficial and empowers communities to be more proactive about their health and health concerns. These approaches as well as the recruitment and retention efforts mentioned earlier are expensive, time consuming, and labor intensive, but they are absolutely necessary to engage a disenfranchised population with high levels of mistrust.

ASSESS A WIDE RANGE OF RISK FACTORS

The third recommendation is to assess a wide range of risk factors. Cognition is multidimensional and composed of several distinct abilities. Since specific brain regions are selectively vulnerable to different age-related diseases (such as hippocampal formation in Alzheimer's disease and the substantia nigra in Parkinson's disease), it is likely that risk factors associated with these diseases will affect some cognitive abilities more than others. In fact, there is a growing appreciation in the literature for this point in the non-Hispanic white population. However, there are few data on risk factors for change in different cognitive abilities among African Americans, and none that link risk factors with neuropathology. Because most studies in the community use brief screening measures to assess cognition, the additional time required to more broadly assess specific cognitive abilities is the biggest cost but is outweighed by the enhanced ability to emphasize dissociable cognitive systems that have different anatomic substrates commonly affected by Alzheimer's disease.

GO BEYOND COGNITIVE FUNCTION TESTS

Finally, cutting-edge antemortem imaging, biofluid biomarkers, and autopsy of people from diverse racial and ethnic backgrounds must be incorporated into studies of prevention. Performance on cognitive function tests is still the gold standard for diagnosing Alzheimer's disease. As discussed, education is closely tied to performance on these tests, and both years and quality of education tend to be lower in racial and ethnic minorities, creating serious challenges for accurate diagnoses in these populations. Given that clinical and pathological information about the earliest cognitive changes is now making it possible to develop strategies to prevent the disease from developing or to slow its progression, the field is primed to advance questions about risk factors for Alzheimer's, and Alzheimer's pathology in the African American population.

Conclusion

The older African American population is growing at a rapid pace, and the burden of aging-related cognitive impairment and Alzheimer's disease will continue to present a tremendous challenge. Studies of substantial numbers of cognitively unimpaired African Americans with well-characterized cognitive data and clinical biomarkers would facilitate correlation of cognitive status with observed neuropathologic changes, allowing scientific questions regarding the accumulation of pathology along the full spectrum of cognitive aging from normal aging to dementia to be addressed in one of the most vulnerable at-risk populations in the United States. What is learned from African Americans will likely lay the foundation of understanding for other racial and ethnic population groups, and for society as a whole.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Exhibit 1

Risk Factors For Cognitive Decline In Population- And Community-Based Cohorts Of Older Adult African Americans And Non-Hispanic Whites

Risk factors that increase risk of cognitive decline	Risk factors that decrease risk of cognitive decline
Depressive symptoms ^{a,b}	Cognitive activity ^c
Diabetes ^{d,e}	Social networks ^f
APOE-e4 ^g	Greater life space ^{h,i}
Perceived stress ^j	Higher body mass index ^k
Smoking ^l	Vitamin E ^m
Psychological distress ⁿ	Vegetable/fruit consumption ^o
Interleukin 6 ^p	Alcohol consumption ^q
Myeloperoxidase polymorphism ^r	Statin use ^s
	Early-life adversity ^{t,u}
	Social engagement ^{f,v}

SOURCES See below. A complete list of sources is available in the online Appendix. To access the Appendix, click on the Appendix link in the box to the right of the article online.

^aWilson RS, et al., Depressive symptoms and cognitive decline.

^bSachs-Ericsson N, et al., The influence of depression on cognitive decline.

^cWilson RS, et al., Cognitive activity and cognitive decline.

^dWessels AM, et al., Diabetes and cognitive decline in elderly African Americans.

^eYaffe K, et al., Diabetes, glucose control, and 9-year cognitive decline.

^fBarnes LL, et al., Social resources and cognitive decline in a population of older African Americans and whites.

^gSawyer K, et al., Racial differences in the influence of the APOE epsilon 4 allele.

^hCrowe M, et al., Life-space and cognitive decline in a community-based sample.

ⁱJames BD, et al., Life space and risk of Alzheimer disease.

^jAggarwal NT, et al., Perceived stress and change in cognitive function.

^kSturman MT, et al., Body mass index and cognitive decline in a biracial community population.

^lReitz C, et al., Effect of smoking and time on cognitive function.

^mMorris MC, et al., Vitamin E and cognitive decline in older persons.

ⁿWilson RS, et al., Proneness to psychological distress (Note 33 in text).

^oMorris MC, et al., Associations of vegetable and fruit consumption with age related cognitive change.

^pEconomos A, et al., Interleukin 6 plasma concentration associates with cognitive decline.

^qWright CB, et al., Reported alcohol consumption and cognitive decline.

^rPope SK, et al., Myeloperoxidase polymorphisms and cognitive decline.

^sSzwast SJ, et al., Association of statin use with cognitive decline.

^tBarnes LL, et al., Effects of early-life adversity on cognitive decline in older African Americans and whites.

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^vRelated to reduced rate of decline only in non-Hispanic whites.