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Models of biomarker relationships in Alzheimer's disease are inconsistent in diverse populations

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Abstract

PET imaging measuring β-amyloid (Aβ) plaques and tau tangles has been utilized to study the underlying pathology of Alzheimer's disease. In addition, other biomarkers such as CSF t-tau, white matter hyperintensities, functional connectivity within the default mode network, and structural MRI measures of neurodegeneration have led to increased knowledge about biological changes associated with Alzheimer's disease. Through the identification of trends between biomarkers in association with Alzheimer's disease, models have been established illustrating the relationship between various biomarkers and Alzheimer's disease; however, the majority of these studies have derived these models from the data of mostly Caucasian populations. Recent studies have identified inconsistencies in the application of current models of Alzheimer's disease on diverse populations, such as African Americans, as levels of a certain biomarker in Caucasians may have different implications on cognition compared to African Americans. Such inconsistencies have the potential to cause the delayed detection of Alzheimer's disease in diverse populations, limiting treatment options. To combat this issue, the lack of diversity in research samples must be addressed. The accumulation of instances of medical exploitation and current eligibility criteria for clinical trials have discouraged participation in research trials among diverse populations, contributing to the health inequity concerning Alzheimer's disease treatment. Furthermore, a number of biological and external disparities must be addressed. Potential methods of addressing such disparities include uniting the National Institute on Aging (NIA) Health Disparities Research Framework with the NIA-Alzheimer's Association Research Framework and expanding research on plasma biomarkers that are more consistent in diverse populations. This review analyzes inconsistencies in the application of Alzheimer's disease biomarker models to diverse populations, namely African Americans, along with potential implications and methods of addressing disparities.

Keywords

Alzheimer's disease, Biomarker, Diverse populations, Amyloid PET, CSF t-tau, White matter hyperintensities, Default mode network

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Introduction

Through the accumulation of research, various measures such as amyloid PET, tau PET, CSF t-tau, structural measures such as neurodegeneration and white matter hyperintensities, and functional connectivity within the default mode network have been identified as valid biomarkers of Alzheimer's disease. Such research has led to the establishment of models illustrating the relationship between such biomarkers and Alzheimer's disease. For instance, the presence of both Aβ plaques and tau tangles have a strong, inverse correlation with cognition (1, 2). Increased levels of CSF t-tau, which serve as measurable proxies for the pathology of Alzheimer's disease, also suggest neurodegeneration associated with Alzheimer's disease with high accuracy (3). Similarly, increases in white matter hyperintensities are associated with the neurodegeneration of Alzheimer's disease (4). Additionally, the majority of studies analyzing functional connectivity within the default mode network have found that reduced connectivity is correlated with Alzheimer's disease (5). Despite this, new studies exhibiting inconsistencies surrounding the application of established models on diverse populations have arisen. Observing CSF t-tau, white matter hyperintensities, and connectivity within the default mode network, researchers have found that equivalent levels of such biomarkers are not associated with the same impact on cognition among diverse populations. As a result, current models of the relationship between Alzheimer's disease and biomarkers have been put into question.

Amyloid PET

The effect of amyloid deposition on neurodegeneration was examined in diverse populations. Such research drew upon the established knowledge of amyloid positivity shown through PET imaging in Alzheimer's disease (6). A particular study demonstrated that elevated amyloid PET signals in African Americans resulted in greater neurodegeneration than Caucasians with elevated Aβ deposition, suggesting that African Americans experience more atrophy than Caucasians. The addition of white matter hyperintensities to the model strengthened this relationship, suggesting that white matter hyperintensities play a role in the increased atrophy found in African Americans (7). Along these lines, an additional study found that cognitively normal non-Hispanic African American subjects had lower rates of amyloid positivity compared to cognitively normal non-Hispanic Caucasian subjects. Notably, a negative correlation was observed between the percentage of African ancestry and amyloid within the non-Hispanic African American group (8). Furthermore, a particular longitudinal study found that amyloid PET accumulated more slowly in African Americans with normal cognition compared to Caucasians with normal cognition, reflecting differences in the progression of amyloid PET in African Americans compared to Caucasians (9). This contributes to the potential for different implications of equivalent amyloid deposition in diverse populations as well as the possibility of a combination of risk factors leading to Alzheimer’s disease.

Cerebrospinal Fluid (CSF) t-tau

Prompted by the discovery of various biomarkers related to Alzheimer's disease along with the lack of diverse samples in previous studies, researchers have investigated

the effect of race on the relationship between biomarkers measures and the development of Alzheimer's disease. While increased concentrations of CSF t-tau as a function of age were documented for both cognitively impaired African Americans and Caucasians, the African American group had a lower overall mean concentration of CSF t-tau compared to the Caucasian group, suggesting that equal levels of CSF t-tau have different implications on different populations (10). This finding was supported by additional research which demonstrated that in African Americans, as cognition declined, smaller changes in concentration of CSF t-tau were observed compared to Caucasians, indicating that small changes in the concentration of certain biomarkers may have a comparably larger impact on cognitive impairment in African Americans than Caucasians (11). Furthermore, a particular meta-analysis of five studies found that CSF t-tau was consistently lower in African Americans compared to Caucasians among subjects with normal cognition, mild cognitive impairment, and Alzheimer's disease (12).

White Matter Hyperintensities

Utilizing the knowledge that an increase in white matter hyperintensities is a risk factor for cognitive decline, the correlation of levels of white matter hyperintensities to Alzheimer's disease biomarkers in diverse populations has been examined (4). Through Multivariate Linear Regression Analysis, a certain study determined that greater cognitive impairment was found in African Americans than Caucasians despite equal amounts of white matter hyperintensity, suggesting that an equal increase in white matter hyperintensity has a greater impact on cognition in African Americans than in Caucasians. In order to determine the validity of CSF sVCAM-1 (a certain CSF vascular biomarker) across diverse populations, levels of the biomarker were examined in relation to white matter hyperintensity volumes. While the concentration of the biomarker increased with increases in white matter hyperintensities in Caucasians, the concentration of the same biomarker saw little change despite the increase in white matter hyperintensity in African Americans. As a result, the CSF sVCAM-1 seems to be only suggestive of cognition in Caucasians as it reflected underlying white matter hyperintensities in Caucasians but not African Americans (11). Furthermore, the disparity between the impact of white matter hyperintensities on African Americans compared to Caucasians amplifies the inconsistencies in the use of the CSF vascular biomarker.

Functional Connectivity Within the Default Mode Network

Another neuroimaging biomarker, imaging of the functional connectivity within the Default Mode Network (DMN), which is involved with episodic memory processing, has been analyzed to research changes in the brain as a result of Alzheimer's disease. Previous research demonstrating the correlation between disruptions in functional connectivity within the DMN and Alzheimer's disease has resulted in the application of this biomarker in diverse populations (5). In a particular study, however, though greater cognitive impairment was associated with decreased connectivity in Caucasians, in African Americans greater cognitive impairment was associated with increased connectivity within the DMN. Furthermore, African Americans and

Caucasians demonstrated disparities in how DMN connectivity was related to CSF Aβ42 and CSF t-tau levels. For instance, lower levels of CSF Aβ42 and increased CSF t-tau correlated with greater connectivity in African Americans while it correlated with decreased connectivity in Caucasian populations (13).

Table 1

Inconsistencies of biomarker relationships in Alzheimer's disease

Biomarker	Relationship with AD	Inconsistencies for African Americans	Ref.
Amyloid PET	Amyloid positivity	↑ signal results in comparably greater neurodegeneration	(6, 7)
CSF t-tau	↑ concentration; neg. correlation with functional connectivity within the DMN	↓ changes in concentration with a comparably ↑ impact on cognition; pos. correlation with functional connectivity within the DMN	(10, 11)
White Matter Hyperintensities	Pos. correlation with risk for cognitive decline	Equal increase has a comparably larger impact on cognition	(4, 11)
CSF sVCAM-1	Pos. correlation with white matter hyperintensities	Little change despite increases in white matter hyperintensities	(11)
Functional connectivity within the DMN	↓ functional connectivity within the DMN	↑ functional connectivity within the DMN	(5, 13)
CSF Aβ42	↓ concentration; pos. correlation with functional connectivity within the DMN	Neg. correlation with functional connectivity within the DMN	(13)

Table 1: Inconsistencies of biomarker relationships in Alzheimer's disease (AD)

Discussion

Lack of Trust in Healthcare

The inconsistencies in the generalization of current cognitive exams on diverse populations demonstrated can be attributed in part to the lack of diversity in research samples that inform present Alzheimer's disease biomarker models. This lack of representation in research results from the general shortage of diverse populations willing to participate in clinical trials, restricting the available data for representative models to be created. A particular study found that African Americans were 64% less willing than Caucasians to be contacted about typical Alzheimer's disease prevention trials which constitute cognitive testing, brain imaging, and blood drawing for subjects, reflecting distrust in the healthcare system among African Americans (14). In

particular, some studies use lumbar punctures to collect cerebrospinal fluid for biomarker research; however, this procedure is invasive and evokes trauma that stems from historic instances of medical exploitation (15).

During the mid-1900s, the US Public Health Service experimented on low-income African Americans to research the "natural course" of syphilis without the informed consent of test subjects. Furthermore, though by 1943, penicillin had become widely available as a treatment for syphilis, treatment was withheld from subjects often causing death. Many 20th-century doctors practiced "benevolent deception", the concept of withholding medical information from patients in order to avoid confusion or worry. Because of this, test subjects were left unaware of the true nature of the study and its associated risk. Also, the prevalence of segregation during this period restricted the job opportunities of African Americans and in turn their ability to support themselves. As a result, African Americans were lured into accepted incentives such as stipends and free meals in exchange for participating in research studies while such mistreatment was kept a secret from the general public. Because of this, the news of the US government's exploitation of African Americans published by the Associated Press in 1972 resulted in massive public objection which ended the study. The Tuskegee Syphilis Study and other instances of racial discrimination have caused distrust in the participation of clinical trials and the healthcare system among African Americans, discouraging African Americans from seeking medical attention compared to Caucasians. Following the end of the Tuskegee Syphilis Study, the probability of African American men visiting a doctor decreased drastically as a function of proximity to the location of the Tuskegee Study. This resulted in the increase of age-adjusted mortality rates for African Americans in close proximity to the Tuskegee Study with a majority of these deaths being caused by health issues rather than external causes. Conversely, no change in mortality rates was seen in Caucasians following 1972 (16).

Eligibility Criteria For Clinical Trials

Current eligibility criteria for clinical trials may discourage diverse participation. A number of requirements often need to be met by subjects in order to participate in clinical trials; however, these criteria exclude diverse populations, leading to underrepresentation (17).

Many clinical trials require that subjects meet a baseline neuropsychological test score in order to participate; however, current neuropsychological tests have a number of inherent limitations. One of the most prevalent barriers to the standardization of neuropsychological tests is language. Neuropsychological tests cannot simply be translated word-for-word as each language has its grammatical and idiomatic nuances. As a result, wording that is ineffectively translated may affect results, particularly in diverse populations. Furthermore, even without translation, neuropsychological tests may use complex language that is unfamiliar to an individual based on one's educational background. The use of stimuli in neuropsychological tests may also cause inconsistencies as some items may be unfamiliar to individuals based on their cultural background (18). As a result, research has

shown that neuropsychological test results are variable based on socioeconomic status, educational opportunities, and geography (8, 19). This suggests that a number of factors may cause inconsistencies in neuropsychological tests. Because of this, many clinical trials have created language fluency, education, and cognitive score requirements (20); however, this discourages diverse participation, potentially skewing the data.

Many clinical trials also excluded subjects with other comorbidities and required caregiver attendance. While these measures attempt to create the most accurate data, they exclude key populations. Firstly, research has shown that comorbidities such as hypertension are more prevalent among African Americans (21). Additionally, African Americans may not have equal access to regular caregivers. As a result, this criteria narrows the diversity in sample size included in research causing inconsistencies (20).

Biological Disparities

Without increased representation in research, the application of inconsistent models may lead to a late or inaccurate diagnosis of Alzheimer's disease in African Americans, limiting treatments available for slowing the development of Alzheimer's disease. Looking at concentrations of certain biomarkers alone, Alzheimer's disease in African Americans may be overlooked because lower concentrations of certain biomarkers are correlated with Alzheimer's disease in African Americans than that of currently established thresholds for Alzheimer's disease which were derived based on mainly Caucasian populations. In order to prevent this, research must be expanded not only on the levels of certain biomarkers in diverse populations, but the implications of these levels in relation to cognition. Additionally, disparities in vulnerability to risk factors for Alzheimer's disease must be considered. A number of diseases such as diabetes mellitus, renal disease, and hypertension have been recorded to be correlated with increased risk for Alzheimer's disease (22). In a particular study, African Americans were significantly more frequently affected by diabetes mellitus, renal disease, and hypertension. Specifically, hypertension played the largest role in racial disparities in Alzheimer's disease risk between African American and Caucasian populations (21). In the diagnosis of Alzheimer's disease and future research, measures accounting for such disparities in vulnerability to risk factors for Alzheimer's disease should be implemented. Furthermore, the possible differences in the brain's structural and functional networks must be considered.

A number of structural differences in total brain volume, hippocampal volumes, cortical thickness, and lateral ventricle size have been found in diverse populations which may contribute to Alzheimer's disease risk. Research has found that African American subjects had larger mean total brain volumes compared to non-Hispanic Caucasian subjects among both cognitively normal participants and those with mild cognitive impairment, which may contribute to the biomarker inconsistencies. Cognitively normal African American subjects also had smaller average hippocampal volumes compared to Caucasian subjects, potentially reflecting inherent biological differences among diverse populations. Furthermore, an additional study found that African Americans with

Alzheimer's disease had smaller hippocampal volumes than Caucasians with Alzheimer's disease, suggesting the persistence of structural differences throughout the progression of Alzheimer's disease. Research has found that African Americans with normal cognition, mild cognitive impairment, and Alzheimer's disease have smaller cortical thickness than Caucasians. This is significant as smaller cortical thickness is associated with cognitive impairment, suggesting a higher risk of Alzheimer's disease in African Americans (23). These biological disparities may cause inconsistencies in Alzheimer's disease biomarker relationships, demonstrating the importance of further research.

External Disparities

Disparities in a number of external risk factors for Alzheimer's disease such as environment, education, and stress should also be taken into account. A particular study found that those living in disadvantaged neighborhoods had a higher risk for Alzheimer's disease, suggesting that factors such as income, education, and housing quality play a role in Alzheimer's disease risk (24). In the United States, in particular, there is a disproportionately greater population of minority groups living in disadvantaged neighborhoods, which may account for disparities in populations affected by Alzheimer's disease. In another study, African Americans reported more stressful life events than Caucasians which was associated with an age-related decline in verbal learning and memory (25). Along these lines, research suggests that perceived stress may contribute to ethnoracial disparities in cognition (26). Such disparities in external risk factors for Alzheimer's disease should be considered in the diagnosis of Alzheimer's disease and future research.

In order to ensure the effectiveness of healthcare through diverse samples, a number of barriers must be overcome. The historical distrust of the healthcare system among African Americans must be confronted. In order to combat this, the research staff of clinical trials should be diversified as individuals are subconsciously more inclined to participate in studies operated by people who share similar cultural backgrounds and can communicate in their native languages. Currently, the award rate for research grants by the US National Institutes of Health (NIH) is 13% lower for African Americans than Caucasians, suggesting that the European majority in research samples reflects the European majority in researchers being funded by the US NIH. This disparity may be fueled by the lack of representation among reviewers for research project grants in the NIH as this group is composed of less than 2% of African Americans. As a result, increasing diversity in the field of medical research has the potential to promote the recruitment of diverse sample sizes. Furthermore, factors that may discourage one from participating in clinical trials such as lack of transportation, childcare, and flexible work hours which may be more prevalent in minorities must be addressed in order to support this effort (27).

Another factor that must be considered is counterfactual fairness or the "intuition that a decision is fair towards an individual if it is the same in (a) the actual world and (b) a counterfactual world where the individual belonged to a different demographic group" (28). Currently, there is no clinical criteria for Alzheimer's disease diagnosis. As a result,

physicians use their own judgment to diagnose Alzheimer's disease which results in inevitable inconsistencies. This is reflected in research that found that African Americans who were diagnosed with Alzheimer's disease exhibited more severe symptoms compared to Caucasians (29). Furthermore, research has found that African Americans individuals were more likely to seek medical attention during advanced stages of Alzheimer's disease compared to Caucasians (30). This may be attributed to the lack of trust in healthcare and the view that memory loss is a normal part of aging that exists among diverse populations (29). These gaps result in lower levels of Alzheimer's disease diagnosis among non-Hispanic African American individuals compared to non-Hispanic Caucasian individuals despite risk factors for Alzheimer's disease being more prevalent in non-Hispanic African Americans (31, 29). Addressing this issue is essential to provide equitable care and mitigate inconsistencies in research.

Addressing Disparities

A number of solutions to address such disparities have been introduced. One of these solutions is uniting the National Institute on Aging (NIA) Health Disparities Research Framework with the NIA-Alzheimer's Association Research Framework. Traditionally, the NIA-Alzheimer's Association Research Framework has been used to define Alzheimer's disease through its pathology. Also known as the amyloid/tau/(neurodegeneration) criteria, this method requires the presence of amyloid plaques and tau tangles in order to be diagnosed with Alzheimer's disease. Compared to current cognitive tests which have many limitations, there are many advantages of attempting to define Alzheimer's disease through pathology; however, many inconsistencies have been observed with this model as equivalent amounts of amyloid plaques and tau tangles may have different implications on cognition depending on race. As a result, the NIA Health Disparities Research Framework attempts to account for social and environmental factors that contribute to Alzheimer's disease which account for disparities in Alzheimer's disease among diverse populations. This model is particularly advantageous as it explores the multidimensional nature of social Alzheimer's disease risk factors as it strives to discover "downstream causes" of "upstream risk factors". Combining the NIA-Health Disparities Research Framework with the NIA-Alzheimer's Association Research Framework has the potential to illustrate the pathological and social aspects of Alzheimer's disease. Visually, this model mirrors that of a "mind map" which has a central idea with details branching out of the main idea. A hypothetical model might have Alzheimer's disease in the center with amyloid deposition, tau pathology, and neurodegeneration branching off of it. Then branching off of amyloid deposition might be cardiovascular risk factors that branches off into stress. Addressing the multidimensional nature of such risk factors has the potential to promote public health policies that account for such gaps (15).

The possibility of using a polygenic risk score to diagnose Alzheimer's disease has been researched. The Alzheimer's disease polygenic risk score was formed by researchers using 22 alleles that have demonstrated a correlation with Alzheimer's disease. When tested, they found that this score was able to predict

memory decline in both non-Hispanic Caucasians and non-Hispanic African Americans (32). However, there are a number of limitations that are important to note. Firstly, many biological and external risk factors contribute to Alzheimer's disease risk. As a result, diagnosing Alzheimer's disease using a polygenic risk score gives a one-dimensional perspective of the disease. Secondly, research has suggested that APOEε4 (the most prevalent genetic risk factor for Alzheimer's disease) may have a weaker effect in increasing Alzheimer's disease risk in African Americans compared to Caucasians (8). It is also important to note that the polygenic risk score was developed on data from genome-wide association studies, where data from diverse populations is significantly limited (33). Because of this, more research is necessary to test its accuracy.

In order to combat gaps in current neuropsychological tests, the utilization of race-based norms has been suggested. This method draws upon normative standards for neuropsychological tests created by a representative sample of people from the same ethnic background. While this may reduce inconsistencies in research, there are a number of drawbacks that must be addressed. Firstly, it is essential that the sample used accurately reflects the diversity that exists within a population in society in terms of factors such as educational background, income, and risk of certain diseases. As a result, such nuances make the utilization of race-based norms difficult to put in place. Furthermore, it may make a number of assumptions that might lead to potentially harmful interpretations of underlying racial differences (34). Instead of using race-based norms for neuropsychological tests, the potential of drawing upon normative standards of Alzheimer's disease biomarkers has been introduced. While current biomarker models generally use a standard cutoff for all populations to diagnose Alzheimer's disease, this idea suggests different cutoffs based on race. However, this idea must also be approached with caution as heterogeneity persists within races. Furthermore, the nature of race itself is fluid as it can be considered a social rather than a biological construct. Because of this, finding a method of Alzheimer's disease diagnosis that is consistent is ideal (35). Research suggests that the plasma Aβ42/Aβ40 biomarker more accurately reflects amyloid PET status compared to other plasma biomarkers. It is important to note, however, that looking at the absolute value of the Aβ42/Aβ40 plasma biomarker may lead to misleading interpretations. Research has found that African Americans had a higher mean plasma Aβ42/Aβ40; however, this was correlated with lower levels of brain amyloidosis compared to Caucasians. In contrast, the levels of other plasma biomarkers such as p-tau181 did not vary by race though African Americans were less likely to be amyloid positive. As a result, Aβ42/Aβ40 has the potential to become a valuable biomarker as it is more consistent in diverse populations (35).

Methods to overcome the eligibility criteria for clinical trials must be developed. To overcome the language barrier in cognitive tests, a system of live translation of test material by research staff was created and used by one study; however, this method requires further development to ensure accuracy (36). Flexibility is also necessary among research staff to prevent inconsistencies steaming from

the caregiver requirement. In practice, such flexibility may take the form of appointments scheduled outside of weekday business hours or remote administration over the phone or by video call (20).

Artificial intelligence has the potential to combat counterfactual fairness, which inhibits Alzheimer's disease diagnosis and treatment for diverse populations. Using artificial intelligence, an algorithm is being developed to target sicker African American patients who might be otherwise overlooked. In the preliminary stages of testing, researchers found that 46% of the patients qualifying for care management were African American compared to the 17% of African Americans who qualified when this algorithm was not applied. Furthermore, by analyzing models that are formed by this algorithm, researchers can potentially identify factors that contribute to counterfactual fairness. However, this algorithm is still in the early stages of development and requires more testing to ensure that it does not make assumptions that perpetuate bias (37).

Increasing the number of longitudinal studies has the potential to help gain the data to better address these inconsistencies. While cross-sectional studies illustrate levels of Alzheimer's disease at one point in time, longitudinal studies can reflect pathological and cognitive changes over the progression of Alzheimer's disease. Because of this, researchers can better differentiate between inherent and progressional differences (34). However, when conducting longitudinal studies among diverse populations, methods must be developed to address dropouts as a study found that African Americans had a higher rate of dropouts. Furthermore, this observation suggests that addressing these elements might increase diverse participation in clinical trials on the whole (38). These barriers must be overcome as longitudinal studies may provide a better image of biomarker changes in Alzheimer's disease in diverse populations compared to cross-sectional studies (34). To accompany such research, efforts to expand outreach to diverse communities for clinical trials must be developed as the disparities in the method of recruitment may account for inconsistencies observed (39). Possible methods include partnerships with local organizations and civic leaders to increase awareness of this issue, facilitating the increase of diversity in samples (28).

Conclusion

Through the identification of trends between measurable substances indicative of certain diseases known as biomarkers and Alzheimer's disease, models have been established illustrating the relationship between various biomarkers and Alzheimer's disease; however, numerous studies have found inconsistencies in Alzheimer's disease biomarker models. Disparities have been observed between levels of CSF t-tau, white matter hyperintensities, and functional connectivity within the default mode network and cognition between Caucasians and African Americans, suggesting that equivalent levels of certain biomarkers can have disproportionate effects on cognition in diverse populations. As a result, it is essential that the public policy issues that fuel such inconsistencies be addressed to create an equitable healthcare system.

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