ALZHEIMER'S, VASCULAR, AND MIXED DEMENTIA IN AFRICAN AMERICAN POPULATIONS: A REVIEW OF METHODOLOGICAL STRENGTHS AND LIMITATIONS OF THE EPIDEMIOLOGIC LITERATURE FROM 1990-2015

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ABSTRACT

ALZHEIMER'S, VASCULAR, AND MIXED DEMENTIA IN AFRICAN AMERICAN POPULATIONS: A REVIEW OF METHODOLOGICAL STRENGTHS AND LIMITATIONS OF THE EPIDEMIOLOGIC LITERATURE FROM 1990-2015

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Dementia, a chronic syndrome and public health concern, remains a disease not fully understood (1, 2). In moving forward more research is needed to prevent, identify causal pathways, and treat dementia (1, 2). Recommendations from the recent National Institute of Neurological Diseases and Stroke-Alzheimer's Disease and Related Dementias (NINDS-ADRD) conference of 2013 rank as a top priority for future research the development of population-based studies of dementia incidence and prevalence in diverse ethnic groups (2). Further, discordant outcomes have been observed in studies examining these metrics in African Americans specifically (3). A methodological issue relevant to studies of African Americans is case ascertainment, with breadth of diagnosis a critical component that can affect the number of cases identified (3). In addition, the state of dementia research as whole is in a transition (1, 2). A review systematically describing case ascertainment strengths and limitations of the epidemiological literature in this population has not previously been performed.

With heterogeneity of methods an issue limiting comparisons between studies, and the state of research in flux, now is an optimal time to examine what can be learned from the methods of past studies. The aim of this review is to address this gap in the literature by examining breadth of diagnostics utilized across studies, systematically describing strengths and limitations of case ascertainment methodology for the three most common types of dementia, Alzheimer's (AD), Vascular (VaD), and Mixed Dementia (MD), of African Americans from 1990 to 2015.

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KEY TO ABBREVIATIONS

AD	Alzheimer's Disease
ADDTC	Alzheimer's Disease Diagnostic and Treatment Centers
CARE	Comprehensive Assessment and Referral Evaluation
CSF	Cerebrospinal Fluid
CSI-D	Community Screening Interview for Dementia
CT	Computerized Tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
HIS	Hachinski Ischemic Score
HRS	Health and Retirement Study
LOAD	Late Onset Alzheimer's Disease
MD	Mixed Dementia
MIS	Memory Impairment Screen
MMSE	Mini-Mental State Exam
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute of Aging-Alzheimer's Association
NIH	National Institute of Health
NINDS-ADRDA	National Institute of Neurological Diseases and Stroke-Alzheimer's Disease and Related Dementias
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association-International Association for Research and Neuroscience Education
SPMSQ	Short Portable Mental Status Questionnaire
VaD	Vascular Dementia

Chapter 1: Introduction

A. Etiologies

I. What Is Dementia?

A. Clinical Definition

Dementia is a syndrome of clinical symptoms that develop due to progressive neurodegeneration (4). Mechanisms not fully understood result in a degradation of cognitive functioning in areas that include: memory, reasoning and judgment, communication, language, concentration, and visual perception (4). Dementia diagnoses are assigned when at least two cognitive domains characteristic of the syndrome are affected in a consistent and severe enough manner to impact an individual's ability to function independently in day-to-day tasks (4). It is the sixth leading cause of death in the U.S., although recent estimates indicate it may now rank third, falling behind only heart disease and cancer (5).

There exists upwards of ten etiologies of dementia. This review will focus on examining the three most common; Alzheimer's dementia (AD), Vascular Dementia (VaD), and Mixed Dementia (MD). When not referring to any one of these three specifically, use of the term dementia will be used throughout. Finally, AD, the most common presentation of dementia (2), is classified into two categories based on age, those under 65 years of age, known as early onset or familial AD, and those over 65, referred to as late-onset AD (LOAD). This review will be specifically concerned with the occurrence of LOAD unless otherwise noted.

B. Pathology

i. Alzheimer's Pathology

Introduced in 1992, the amyloid beta cascade hypothesis suggests amyloid beta (AB) as the causative agent of AD (6). AB is a protein formed when a beta variant of secretase cleaves a protein known as the amyloid precursor protein, or APP (7). These secretases are enzymes involved in "cutting" sections of proteins traveling across cell membranes. Once cleaved, they

become known as AB fragments. When AB fragments combine, they can form the larger amyloid beta aggregates implicated in AD. It is hypothesized that these aggregates of amyloid beta then disrupt cell functioning, resulting in neurodegenerative sequelae. In regards to LOAD, this hypothesis has remained controversial (8). Specifically, the debate revolves around whether AB is an upstream or downstream agent to the development of AD. Current research suggests AB as an upstream agent, with its role being necessary, but not sufficient (8).

ii. Vascular Pathology

Any event that blocks or disrupts the flow of blood, which carries oxygen to the brain, has the potential to cause cell death (9). Multiple vascular pathologies are associated with damage to blood vessel structure. These include: cerebral amyloid angiopathy, cerebral atherosclerosis or small vessel disease (often caused by hypertension), and blood-brain barrier dysfunction (10). These can cause neuronal injury leading to cognitive impairment by disrupting cerebral blood vessels and altering cerebral perfusion pressure (blood flow to the brain) (10).

iii. Mixed Pathology

As the name implies, mixed pathology refers to instances where more than one type of pathology exists in the brain concurrently. More often, the term is used to describe the occurrence of both AD and vascular disease (10). With vascular risk factors more common compared to non-Latino Whites (11), we might expect a greater occurrence of mixed dementia pathologies to occur in African Americans. A recent study of autopsy cases supports this, observing that 20% of African Americans autopsied presented with single or pure pathology of either AD or VaD, versus 42% for non-Latino Whites. Meanwhile, in the same study mixed pathology was found in 71% of African American cases, as opposed to the 51% found for non-Latino Whites (12).

II. Current and Projected Burden in African Americans

Current evidence suggests that African American populations are disproportionately affected by dementia (3). It has been proposed that the higher occurrence of cerebrovascular

risk factors such as hypertension (13), obesity (14), and diabetes (15) in African American populations, when compared to that of Non-Latino Whites, for example, may support a hypothesis expecting higher incidence and prevalence, specifically of the dementia subtype vascular dementia, in this population (16).

Multiple epidemiological concerns, such as distributions of disease, are relevant to the aforementioned. First, the exact burden of disease in African Americans remains uncertain, with a wide-range of estimates for the occurrence of dementia for incident and prevalent cases among population-based studies (17). Second, sustained annual increases of the population size of African Americans are expected in the coming decades (18). In addition the average life expectancy is projected to continue to extend well past 65 in coming years for this population (19). Further, advanced age is one of the strongest known correlates to the occurrence of dementia, with incidence and prevalence numbers doubling every five years after the age of 65 (20, 21).

Finally, demographic shifts, with a greater proportion of elder members as well as African Americans making up the general population of the U.S., are expected over the coming decades (22). Taken together these forecasts suggest that even greater numbers of African Americans may develop dementia in coming decades. In conjunction with increased life expectancy, those afflicted could also live longer with the effects of the disease if innovative prevention and treatment methods are not developed.

B. Case Ascertainment

Case ascertainment of dementia is generally a three-step process beginning with the use of screening instruments for base identification of cognitive impairment. This is followed by rigorous neuropsychological test batteries, and culminates in diagnosis of dementia and type of dementia using final syndromic and etiologic criteria, respectively. Use of the term case ascertainment will refer to all phases (screening, neuropsychological batteries, final syndromic and etiologic criteria) together unless otherwise noted. In addition, as it is the most often

reported and often most thoroughly characterized etiology, the following sections will refer to case ascertainment methods used in identifying AD unless otherwise noted.

I. Screening Instruments

While no gold standard for screening exists, there are multiple instruments found to be valid for determining cognitive impairment status in population-based studies. An example of a commonly used instrument for screening is The Mini-Mental State Examination (MMSE). Developed by Folstein et al. (23), the MMSE is a relatively expedient tool, requiring less than ten minutes to administer. The contents of the 11 questions contained therein measure the cognitive domains of orientation, registration, attention and calculation, recall, and language (23).

II. Neuropsychological Batteries

If a specific threshold of cognitive impairment has been met, participants move to a more thorough and comprehensive phase referred to as the neuropsychological battery. As the name implies, a battery of tests are implemented, further assessing domains tested in the screening phase, as well as adding additional domains to form a more comprehensive picture as to the full extent of impairment. For example, domains assessed in this phase can include but are not limited to: memory, orientation, language, reasoning, and visuospatial ability. As with the screening phase, this phase is not specific to assessing any etiologies. Another similarity to screening instruments is the lack of a gold standard for neuropsychological batteries.

III. Final Syndromic and Etiologic Criteria

The final steps for case ascertainment are determining a diagnosis of dementia and dementia type using final syndromic and etiologic criteria, respectively. Generally, this entails either study authors, specialty consultants, such as neurologists and psychiatrists, and or a consensus panel convening at conferences, assigning a diagnosis using the Diagnostic and Statistical Manual of Mental Disorders (DSM), for dementia in general, or the National Institute of Aging-Alzheimer's Association NIA-AA criteria, specifically for AD. During the period covered

by this review, multiple iterations of both of the aforementioned instruments, which are considered gold standards for this phase, were introduced for the final step in the diagnostic process. The DSM, with versions III-R, 1987 (24), IV, 1994 (25), IV-R, 2000 (26), and the DSM-V, 2013, (27), and the NIA-AA criteria, 2011, (29), previously known as the National Institute of Neurological Disorders and the Alzheimer's Disease and Related Disorders (NINDS-ADRDA) criteria, 1984 (28). In addition, it should be noted that the NIA-AA criteria as a gold standard for diagnosis of AD applies to pre-mortem diagnosis, while currently the only way to confirm a definite case remains neuropathologically via autopsy. Versions of the DSM prior to the most recent revision (DSM-V, 2013) possessed a requirement of memory plus one, that is, a level of impairment significant enough in both the memory domain and one other relevant domain, such as aphasia, which is loss of ability to speak or write, and apraxia, or difficulty performing purposeful movements, though not lacking the ability to do so, to be diagnosed with dementia.

Etiologic diagnostic criteria for VaD and MD are, when compared to syndromic criteria, variable and in some respects less concrete, as there currently exists no gold standard, or method "widely agreed upon as being the best available" (66), for either etiology. The identification of VaD etiology in vivo, however, such as evidence of stroke or blood vessel abnormalities, can be identified relatively well using magnetic resonance imaging (MRI) and computerized tomography (CT) scans. Often utilized for the diagnosis of VaD are instruments such as The Hachinski Ischemic Score (HIS) (30), which consists of assigning a score of a one or a two towards 13 clinical features believed to be associated with vascular dementia, such as abrupt onset and evidence of associated atherosclerosis (30), and the DSM criteria mentioned above, of memory plus an additional domain impairment. Other instruments used to diagnose VaD have included The Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) (31) as well as the National Institute of Neurological Disorders and Stroke-Association-International Association for Research and Neuroscience Education (NINDS-AIREN) (32). Mixed dementia, which is often also referred to as multifactorial dementia, has been diagnosed using the same

criteria mentioned for VaD, as well as additional instruments such as the International Classification of Disease, Ninth (1990-1998) (67) and Tenth Revision (1998-current) (33). As an example of the variability of both the conceptual as well as diagnostics for MD, the ADDTC refer to mixed pathology as AD with cerebrovascular disease (31).

In addition, rates for consent of organ donation for autopsy purposes have been observed to be lower in African Americans (34). With cognitive testing being the primary standard for diagnosis in most cases (3), this is of particular importance to studies of Alzheimer's, where a definite diagnosis is only possible via corroboration of clinical diagnostic criteria with examination of brain pathology after death (35).

C. Aim

The aim of this review is to address this gap in the literature by examining breadth of diagnostics across studies, systematically describing strengths and limitations of case ascertainment methodology for the three most common types of dementia, Alzheimer's (AD), Vascular (VaD), and Mixed Dementia (MD), of African Americans from 1990 to 2015. The process for this will involve describing study design, examining case ascertainment methods, and their relationships to the rates of occurrence of AD, VaD, and MD observed for African Americans.

Chapter 2: Methods

A. Source Article Identification

To identify articles for this review initial efforts were formulated to utilize as many search engines as possible, including Pubmed, Google Scholar, Embase, and Thomson Reuter's Web of Science (formerly ISI Web of Knowledge). Upon conferring as advised by the literature (36) with the department liaison to the campus-wide library resource at MSU, Abe Wheeler (37), it was determined that searching Pubmed and Embase would maximize procuring relevant articles while simultaneously minimizing redundancies (36, 38). Pubmed was searched using MeSH (Medical subject headings) terms. MeSH is the National Library of Medicine index developed and maintained to provide a uniform vocabulary for searching the biomedical literature (39). In addition the following delimiters were utilized: years: 1990-2015, species: human studies, study participant ages: 45-64, 65+, types of articles: journal articles, observational studies, and reviews.

In conjunction with the aforementioned, an algorithm was developed using the search terms of interest in combination with a template developed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), as described in their explanation and elaboration document (40). These terms were chosen at the author's discretion. The search terms entered into the aforementioned algorithm include: African Americans, Alzheimer's disease, dementia, diagnosis, Epidemiology, Mixed Dementia, and Vascular dementia.

B. Inclusion/Exclusion Criteria

Articles from the year 1990 to 2015 were examined. To include those diagnosed with late-onset alzheimer's, which is the majority diagnostic outcome of cases in the U.S. (1, 2), and to include those studies examining participants in possible prodromal periods leading up to potential diagnosis; those over the age of 50, with a diagnosis of possible, probable, or definite AD as well as a diagnosis of either Vascular or Mixed Dementia were included. Prevalent, as well as incident cases of the three aforementioned forms of dementia were included. Subjects

must be designated as African American or Black (self-report or otherwise) to be included. Studies that were at least in part population-based were included. Thus, studies utilizing solely institutionalized populations were not included. This was done in order to increase external generalizability of the results for this review. An inquiry in March of 2015 to senior authors of papers initially recovered was sent out with the purpose of nominating additional studies to be added.

Chapter 3: Results

A. Etiologies

A total of 12 epidemiological studies were found examining dementia in African American populations. Five of these twelve, the studies by Demirovic et al. (41), Gurland et al. (42), Hall et al. (43), Katz et al. (44), and Tang et al. (45), focused solely on AD. Two, Perkins et al. (46), and Evans et al. (47) on both AD and VaD. The studies by Fillenbaum et al. (48), Fitzpatrick et al. (49), and Folstein et al. (50) examined all three etiologies, AD, VaD, and MD. Finally, the study by Heyman et al. examined vascular dementia, however, for the remainder of this cohort non-differentiated dementia rates were given (51). The studies by Perkins, Fillenbaum (48), and Gurland (42) examined both incidence and prevalence rates, while Tang (45), Evans (47), Fitzpatrick (49), and Katz (44) examined incidence solely, and Folstein (50), Heyman (51), Hall (43), and Demirovic (41) examined prevalence only. A summary of type of dementia by study can be seen in Table 1, while a summary of sample frame sources, target population, response rates, and the number of participants at baseline can be found in Table 2. Similarly, a map of the U.S. highlighting target populations can be seen in Figure 1. All information in the following tables refer specifically to the results of the African American contingent and the African American contingent only of the studies reviewed, unless otherwise noted.

B. Case Ascertainment

I. Screening Instruments

Across the 12 studies compiled for this review there were five screening instruments used. The MMSE (23) was most often utilized being the primary screener in four of the studies (41, 46, 49, 50). The Short Portable Mental Status Questionnaire (SPMSQ) (51) was used in three studies (41, 48, 51), the Comprehensive Assessment and Referral Evaluation (CARE) (52) screening questionnaire in two studies (42, 45), and the two remaining screening instruments, the Community Screening Interview for Dementia (CSI-D) (53) and the Memory

Impairment Screen (MIS) (54), were used by a single study each, (43) and (44), respectively. The study by Evans et al. (47), simply states that, “Cognitive testing was used to stratify sampling, rather than as a screening test”, without naming any specific screening instrument. A summary of screening instruments used across all studies can be seen in Table 3.

II. Neuropsychological Batteries

Due to the vast heterogeneity in instruments used for the second phase towards case ascertainment, a summary as is provided for both screening instruments as well as final syndromic and etiologic criteria for diagnosis was beyond the scope of this review. To give some sense of context for this review, the content and breadth of batteries were variable from as basic as reporting that, “extensive medical, neurologic, and psychiatric evaluation by respected specialists; genetic testing, MRI” (41), to up to 12 different tests being administered, including multiple tests for language, memory, and general reasoning ability (45).

III. Final Syndromic and Etiologic Criteria

The DSM syndromic criteria and subsequent iterations (III-R, IV, and IV-R) were utilized for diagnosing dementia in general (26, 42, 43, 44, 46, 48, 49, 50, 51), while the etiologic criteria of the NINDS-ADRDA (55) were utilized for diagnosis of AD (26, 41, 43, 44, 45, 46, 47, 48, 49, 51). VaD was diagnosed using California criteria for VaD (49), the international classification of disease (ICD) version 10 (43) and the Hachinski Ischemia Scale for IVD (ischemic vascular dementia) (46). An overall summary of final syndromic and etiologic criteria can be seen in Table 3A. Similarly, a timeline of the diagnostics highlighting both the standards for final syndromic and etiologic criteria can be seen in Figure 2.

C. Occurrence of Alzheimer’s Disease, Vascular, and Mixed Dementia

I. Alzheimer’s Disease

AD was the most thoroughly characterized dementia etiology. Thus, information in the following two tables are concerned solely with AD, while the much more limited data available for VaD and MD are presented afterwards. A summary of incidence and prevalence rates for

Alzheimer's in the African American contingent of studies can be seen in Tables 4 and 5, respectively.

II. Vascular Dementia

Incidence and prevalence rates for VaD were not only limited but variable. Studies by Evans et al (47), Fitzpatrick et al. (49), and Heyman et al. (51) reported incidence rates of 3.0%, 1.3%, and 0.6% for VaD, respectively. Fillenbaum et al., on the other hand, offered simply a proportion of all dementia cases of African Americans in their study classified as incident cases of VaD, 17.8% (48). Similarly, Perkins et al. (46) also gave a proportion for VaD cases out of all dementia cases in their study, however, they did not specify separate results for the African American contingent of their study, simply offering that 55% of all incident dementia cases (including both African American and non-Latino Whites) were of vascular etiology. The sole prevalence provided for VaD came from Folstein et al. (50), who reported a rate of 2.7% among their African American participants.

III. Mixed Dementia

Estimates of MD were even more limited, with only three studies offering any data on either incidence or prevalence. One of the two incidence rates reported came from Fillenbaum et al. (48), which offered data among their African American participants only as a combined percentage of both AD and mixed, at 69%. Fitzpatrick et al. reported an incidence rate of MD cases of 1.5%, but this number is only specified as with or without AD (49). Finally, Folstein et al. reported a rate of 0.6% prevalence for the African Americans in their study (50).

Chapter 4: Discussion

The aim of this review was to examine dementia studies of African American populations from the year 1990-2015, specifically breadth of diagnosis utilized across studies, and their possible contribution to the variance seen in both incidence and prevalence rates. The process for this involved identifying strengths and limitations by describing study design, examining case ascertainment methods, and their possible relationships to the rates of occurrence of AD, VaD, and MD observed for African Americans.

A. Main Findings

Overall, relatively few studies examining dementia in African American populations were found. Of a total twelve studies, eleven examined occurrence of AD, with the sole exception being Heyman et al. (51). Average length of follow-up was variable across studies examining incidence, with data on the mean age of participants often unavailable (see Tables 5 and 6). Even fewer instances were observed for estimates of either VaD or MD, with only a third of studies providing either incidence or prevalence rates for the second and third most common forms of dementia in the U.S. The studies by Evans (47), and Heyman (51), both examined VaD, while Fitzpatrick (49), and Folstein (50), both examined VaD and MD. Remaining studies provided additional data regarding VaD and MD, however, this was limited to non uniform crude proportions from Fillenbaum (48) and Perkins (46).

All studies utilized population-based sample frames, with the exception of the studies by Evans et al. (47), Fillenbaum (48), and Gurland et al. (42), which included both population-based and institutionalized participants. Examining sample frames also revealed that portions of the U.S. African American population remain entirely unrepresented for data on AD rates. Particularly the southeastern states of Alabama, Georgia, Mississippi, and Louisiana, that, according to the 2010 census, contain some of the largest concentrations of African American residents in the U.S., with proportions ranging from 25% (Alabama) to just under 40% (Mississippi) (59).

For VaD and MD, an even greater paucity of studies was observed. Locations without data for AD, such as the aforementioned states of Alabama and Mississippi, also lacked estimates for VaD and MD. In addition, New York, which, when examining the incidence data across studies compiled for this review was found to be one of the more thoroughly researched locations with a fourth of studies, Gurland (42), Tang (45), and Katz (44) estimating AD of African Americans, produced no estimates for either VaD or MD.

Examination of screening instruments revealed inconsistencies in their usage across studies, with no obvious gold standard. Of screening instruments employed from 1990-2015 in studies of dementia in African Americans, the MMSE was utilized most often, in four out of twelve studies (41, 46, 49, 50). However, no temporal trends were observed for the use of screening instruments (Table 3) over any time intervals covered by this review, with, for example, the MMSE being utilized by studies reviewed in the years 1991, 1997, 2003, and 2004.

Use of final syndromic and etiologic criteria, compared to the variability of screening instruments used, were relatively more uniform. The final phase of the diagnostic process ideally progresses from identifying dementia in general, or base dementia, to a specific etiology (relevant to this review, either AD, VaD, MD). The DSM III and IV criteria were utilized in 9 out of 12 studies, while 10 of 12 studies, utilized the NINDS-ADRDA criteria for diagnosing AD during the same time period. Additionally, 3 out of 12 studies did not identify base dementia using the DSM prior to identifying AD (41, 45, 47). .

Incidence rates were variable from 1.6% (95% CI: .47-2.4) for the study by Perkins et al. (46) to 8.2% for the study by Gurland et al. (no CI available) (42). Temporally, there was a trend in incidence of AD over the period 2001-2012 including four studies with rates for African Americans falling within the 3-4% range, along with average length of follow-up ranging from 4-7 years (44, 45, 47, 49). Comparatively, the two remaining incidence rates were larger, estimated at 5.8% (95% CI: 2.6-9.0) and 8.2% (95% CI: N/A), respectively (48, 42). Additionally, average

length of follow-up was shorter for both studies, with 1.5 and 3 years, respectively (42, 48).

Prevalence rates were variable from 4.0% for Folstein (50) to 14.4% (the male cohort of Demirovic et al., 41). Of particular note are the two studies by Hall (43), which, as mentioned previously, were the only instances found that examined African American populations exclusively. While prevalence rates of the remaining studies in this review were quite variable, the two studies by Hall, using similar methods, including the same screening instrument, and final diagnostic criteria for AD (DSM followed by NINDS-ADRDA), returned dementia prevalence estimates of 6.8% (95% CI: 5.8-7.7) for 1992, and 7.5% (95% CI: 4.3-10.6) for 2001, respectively. Further, the authors concluded that the difference between these two prevalence proportions were not significant. The prevalence rates of the remaining studies, however, were less consistent. While five of seven studies did contain rates in the 4-8% range, with overlapping 95% CI's, the rates in the remaining two studies, were much higher, with a 16% prevalence for the study by Heyman et al. (51), and 14.4% for the male segment of the Demirovic cohort (41).

B. Strengths and Limitations

A strength observed across studies was consistent utilization of stratified random sampling methods, with only a few exceptions. This allows for participants to be randomly sampled, reducing potential selection bias. Further, random sampling by strata enables recruitment proportional to variables of interest, and similarly reduces the potential for selection bias of specific variables such as age and other risk factors.

While most studies did utilize stratified random sampling, a limitation was that only a third, the studies by Gurland et al. (42), Fitzpatrick et al. (49), Perkins et al. (46), and Folstein et al. (50) calculated standardized rates. Standardization allows for comparison of rates between studies with varying age distributions. Standardization for those lacking such rates would be possible if age-stratified rates were available for African Americans in each study. However, along with missing subgroup specific information for sample frame and response rates (42, 44, 45, 46, 49, 50, 51), age-stratified rates were not always available (41, 46).

Three studies, Perkins, Fillenbaum, and Gurland, measured both incidence and prevalence as part of their studies. None of the three specified whether there were protocols for addressing incident cases being recounted later as prevalent cases. Both studies by Fillenbaum and Gurland utilized similar measures for determining incidence and prevalence, with point prevalence measures taken at baseline, while those categorized as not demented at baseline were then followed up for the duration during which if they developed dementia were diagnosed as incident cases. The study by Perkins, while similarly determining the presence of pre-existing dementia at one point in time, baseline (point prevalence), in addition utilized retrospective data to determine incidence rates, from the time of retirement for their municipal workers cohort (1980-1984) to the time of the study, 1991. The utilization of retrospective data for case ascertainment of incident cases carries the potential for biases often associated with case control studies, such that determination of incident status is dependent on participant recall, and prone to recall bias, as opposed to use of more objective, clinical measures.

Shared target populations was a strength in that it enhanced the ability to compare results across studies. Three of the seven studies examining incidence shared a target population of the state of New York (42, 44, 45). Similarly, the importance of age for being able to compare strata, particularly with the occurrence of dementia doubling every five years starting at the age of 65 (20, 21), saw five of the seven studies of incidence examine the same age range of greater than or equal to 65 years of age (42, 45, 47, 48, 49), with only one study not including the 65-70 age range (44).

An additional limitation observed was that many screening instruments, such as the MMSE, were developed using non-Latino White participants, limiting their validity when utilized for screening African Americans, raising concerns of possible information bias (56). No evidence was found to suggest that any of the screening instruments reviewed were specifically developed or adapted to assess cognitive impairment in the presence of dementia in African Americans. This creates an overarching issue concerning potential differential misclassification

resulting from unaccounted for differences in the cultural background of those being studied, which is seen as a significant aspect of defining ethnicity (57). For example, as previously mentioned both the MMSE and SPMSQ have produced acceptable measures of sensitivity and specificity in identifying cognitive impairment in the presence of dementia. However, these results were produced using non-Latino White populations. Thus, to account for differences related to background, authors will often adjust screening instruments for education levels in their study sample (56). Differences related to ethnicity, race, and culture, however, have persisted in MMSE performance both before and after adjustment for education (56). This could suggest that education is being utilized as a proxy for factors unaccounted for here, such as literacy, years of education, or quality of education (16).

What appeared to be the most significant limitation found involved differences in domains used in versions III and IV of the DSM and NINDS-ADRA criteria (i.e. the more exclusive criteria for older versions of the DSM, etc.), with concerns that information bias in the final step of the diagnostic process may also play a part in the variable AD rates observed. The inclusiveness or exclusiveness of case definition in dementia studies can play a role in the size of resulting incidence or prevalence estimates (58). For instance, Sheshadri et al. observed that case definition using the syndromic criteria of the DSM III and IV requires a level of cognitive decline affecting the ability to function independently in day-to-day-tasks, and is generally assessed using interview with an informant (58). In contrast, the NINDS-ADRDA (28) etiologic criteria measured cognitive decline using medical history gathered from the study participant, sometimes, but not always employing informant input, while documentation of decline is performed using cognitive tests (58). In this context the DSM criteria, specifically the DSM-III-R (24) and DSM-IV (25), are considered to be more exclusive in their towards diagnosis, when compared to the NINDS-ADRDA (28). In addition these versions of the DSM included the memory plus one component discussed earlier. As a result, studies utilizing versions III-R and IV of the DSM could have excluded a portion of cases that would otherwise be classified as

dementia using the NINDS-ADRDA (28). This may have resulted in larger prevalence or incidence estimates for studies diagnosing cases using only the NINDS-ADRDA criteria.

This discrepancy could, for example, help to explain the relatively high proportion of cases in the study by Demirovic et al. (41), who utilized the NINDS-ADRDA criteria solely for diagnosis of AD. The authors reported one the largest prevalence proportions of all studies reviewed with 14.4% for African American men (41). It has been observed that the use of different final diagnostic instruments across studies can have an effect on rates of prevalence observed (58). This could contribute to explaining the variance of rates observed in this review, as ten of the studies (26, 41, 43, 44, 45, 46, 47, 48, 49, 51) utilized the NINDS-ADRDA etiologic criteria and nine (26, 42, 43, 44, 46, 48, 49, 50, 51) utilized the final syndromic criteria of the DSM for diagnosis. However, Heyman et al. (51) utilized both the DSM and NINDS-ADRDA criteria, and still produced the second-highest prevalence rate observed. Additionally however, Heyman et al. also had the smallest sample size, with 83 participants, which also could have contributed to an inflation of prevalence rates. Finally, only the study by Katz et al. included information on autopsy (44). As the only way to verify definite AD, pathological confirmation is important in establishing both the positive and negative predictive value of diagnostic tests (59).

When looking to the diagnosis of VaD and MD, a similar concern is observed. Fortunately, the four studies, both Halls (43), Perkins, (46), and Fitzpatrick (49) did identify base dementia using the DSM criteria, prior to utilizing the NINDS-ADRDA etiologic criteria for identifying AD. Had they not, the concern would be that those not meeting the memory domain impairment requirement characteristic of a final syndromic diagnosis utilizing the DSM that otherwise meet etiologic VaD diagnostic criteria would not be categorized as having dementia, thus potentially removing them from further diagnosis, resulting in underestimating the number of VaD cases. Criteria for VaD are often focused around the domain of executive function. While memory concerns do play a part in diagnosis for VaD, impairment of this domain is not required, as opposed to the DSM-III-R and DSM IV criteria, which require a significant impairment in the

domain of memory to be diagnosed with dementia. For the diagnosis of VaD, which is almost exclusively specified as an etiology after a base diagnosis of general dementia, those not initially meeting the requirement of memory plus one yet meeting criteria for VaD would not move on to diagnosis of specific etiology. This could be particularly relevant for African American populations, where vascular risk factors are more common (3), as it may underestimate the occurrence of VaD in this population.

An additional limitation is possible regional variation of proposed risk factors, such as hypertension, diabetes, and obesity, which have been observed to be more common in African Americans (13, 14, 15). These risk factors are found in higher numbers in these same southeastern states that currently lack data for incidence and prevalence of dementia in African Americans, along the so-called “stroke belt” (60). Lack of specific risk factor information relevant to African Americans for multiple studies in this review, as well as inconsistencies in which risk factors are included across studies further limits the ability to compare rates across studies.

While this review aimed to provide an overview on breadth of diagnosis and the state of case ascertainment methods in studies of AD, VaD, and MD etiologies of dementia in African Americans, there were limitations. By focusing on case ascertainment, for example, other relevant concerns such as risk factors were not emphasized. While examining causal pathways was not an aim of this review, the importance of variable risk factors should not be overlooked, especially considering the current state of change dementia research is undergoing, one where inclusion of risk factors previously thought relevant to the development of dementia are being re-examined as to their exact roles in the causal processes, along with exploration of risk factors previously not considered, and implementation of more objective measures are being explored (1, 2).

C. Further Studies

The use of nationally representative study samples, such as those available in the Health and Retirement Study (HRS) (65), that includes measures of cognition that can be used

in studies of dementia, could help mitigate some of the difficulties inherent to initiating or reproducing multiple large studies (costs, time, etc.) which are needed to sample African Americans across different parts of the country. Additionally, with the suggestion that disease course may differ for African Americans when compared to other ethnic/racial groups, only including point prevalence estimates could limit the ability to examine interval trends in rates of dementia when compared to collecting repeated prevalence measures over the course of longitudinal studies (3). As the HRS database is updated with new survey data every two years, utilizing this data could be a resource worth investigating for accessing more current data for the study of dementia in African Americans. However, whether the nationally-representative sampling method used in the HRS adequately takes into consideration the potential for proportional differences in risk factor occurrence, such as the higher rates of hypertension, diabetes, and stroke among African Americans of the southeastern portion of the U.S, should also be considered.

In addition, vascular risk factors are an elevated concern for African Americans (3). Thus inclusion of AD, along with both VaD and MD would ideally be prioritized when studying dementia in this population going forward. Integral to the all of this is the establishment of evidence on risk factors for dementia in African Americans. Aiming towards the development of a consensus on risk factor data could also be collected when examining incidence and prevalence rates, which may help to refine etiological hypotheses for AD, VaD, and MD in African Americans going forward.

In addressing screening instruments future research could be refined by utilizing the relatively recent introduction (2013) of the National Institutes of Health (NIH) Toolbox (63). The NIH Toolbox has a component for assessing cognition and was developed to be utilized in studies with participants of diverse backgrounds (63). Utilization of the NIH Toolbox as a standardized screening instrument across future studies could assist in producing more readily comparable outcomes by mitigating the incompatibility of comparing rates produced using

fluctuating screening instruments of variable sensitivity and specificity across studies. In general, the use of more objective markers for disease could help mitigate these concerns.

While issues inherent to the use of variable instruments for final diagnostic criteria are no longer relevant for current versions, this does not alleviate the fact that current rates of incidence and prevalence available are at least in part based upon incompatible diagnostic methods. This means that a number of studies included in this review could be outdated in a diagnostic sense, and new studies may need to be performed with similar populations but using the current versions of instruments for final diagnostic criteria for dementia. Also, shifting demographics as well as the potential for previous data to be outdated, with only one of twelve studies having occurred less than 12 years ago (44), also help make a case for new studies of the target populations examined in this review. Emphasis towards standardization including advocating for a process including base diagnosis of dementia utilizing the DSM criteria, followed by differential diagnosis of specific etiologies, could ultimately enhance researchers ability to compare results across studies. Analysis to assess the extent of the impact these differing criteria could have had on the resulting rates of dementia could also be investigated.

The addition of more objective methods for diagnosis introduced subsequent to publication of the studies reviewed, such as biomarkers of cerebrospinal fluid (CSF), and use of refined imaging methodologies, e.g. Magnetic Resonance Imaging (MRI), when applied in a standardized manner for case ascertainment criteria, could mitigate issues faced from relatively subjective case ascertainment methods reviewed here, with potential to produce more accurate anti-mortem estimates of dementia in African Americans.

Finally, the inclusion of age-stratified rates or age distributions as a standardized item for studies could supplement variable length of follow-up info, to allow for a sense of being able to calculate whether age stratified rates *across studies* are comparable.

D. Conclusions

Development of new studies examining dementia of African American populations are

sorely needed, as existing studies are outdated in terms of case ascertainment instruments utilized, and potentially for population characteristics assessed, such as risk factor data. Emphasis on new studies examining AD, VaD, and MD simultaneously could expedite further research and allow for comparisons to be made consistently between studies for the three most common dementia etiologies of African Americans.

If the recommendations suggested here are adopted, larger, clinically well-characterized longitudinal cohorts could be created and compared, which may aid in guiding future researchers in establishing the validity of a connection between vascular risk factors and dementia of African Americans. The implication being that if this connection can be established, then public health efforts can be directed towards a targeted reduction of vascular disease by addressing these modifiable risk factors, which could lead to a significant impact on the occurrence of dementia in African American populations (3).

Lack of data on incidence pertaining to African Americans from southern U.S. states currently limits the ability to assess risk, and therefore to develop and tailor relevant recommendations for preventative measures. Similarly, lack of data on prevalence estimates from these areas limits the ability to appropriately address service needs for those currently affected. Therefore, either the use of and standardization of pre-existing instruments developed for use in diverse populations for screening, such as the NIH Toolbox, or adaption and validation of pre-existing instruments for use in African Americans is required. In addition, the creation and refinement of more objective measures of disease burden are highly recommended.

Another consideration is the possibility that the rates of previous studies, while varying significantly across studies for African American populations, could be in line with reality, and may reflect the variation of contributing factors relevant to subgroups of African Americans living in various locations of the U.S. In addition to supporting the NINDS-ADRDA conference and AD Research Summit goals in conceptualizing creation of new studies of incidence and prevalence,

utilization of the methods outlined in this review for the creation of state of the art studies could help clarify whether that may be the case, or whether inconsistent methods used across previous studies, or a combination of factors such as geographic variation of risk factors combined with inconsistently applied, non subgroup-validated methods, can help explain the large variation of rates of AD, VaD, and MD in African Americans.

APPENDIX

Table 1: Types of Dementia by Study

Study	Year	*Hybrid**	*Alzheimer's*	*Vascular*	*Mixed*
Folstein et al.	1991	-	✓	✓	✓
Heyman et al.	1991	-	-	✓	-
*Hall et al.***	1992	-	✓	-	-
Perkins et al.	1997	-	✓	✓	-
Fillenbaum et al.	1998	✓	✓	✓	✓
Gurland et al.	1999	✓	✓	-	-
*Hall et al.***	2001	-	✓	-	-
Tang et al.	2001	-	✓	-	-
Demirovic et al.	2003	-	✓	-	-
Evans et al.	2003	✓	✓	✓	-
Fitzpatrick et al.	2004	-	✓	✓	✓
Katz et al.	2012	-	✓	-	-

*Hybrid refers to inclusion of a study sample composed of both population-based and institutionalized participants
**Hall 1992 and Hall 2001 belong to the same article (43), though separated in tables

Table 2: Sampling Summary of African Americans

Study	Year	*Location**	*Frame***	*Response****	*n*
Folstein et al.	1991	East Baltimore	-	-	210
Heyman et al.	1991	North Carolina	-	-	83
Hall et al.	1992	Indiana	2582	86.0%	2212
Perkins et al.	1997	Texas	-	-	682
Fillenbaum et al.	1998	North Carolina	2261	79.0%	1775
Gurland et al.	1999	New York City	-	-	729
Hall et al.	2001	Indiana	4260	44.0%	1892
Tang et al.	2001	New York City	-	-	610
Demirovic et al.	2003	Florida	827	71.0%	586
Evans et al.	2003	Illinois	554	67.6%	373
Fitzpatrick et al.	2004	CA, MD, NC, PA	-	-	492
Katz et al.	2012	New York	-	-	350

*Target population
**Sample frame
***Response rate

Table 3: Screening Instruments

Study	Year	*MMSE*	*SPMSQ*	*CARE*	*CSI-D*	*MIS*
Folstein et al.	1991	✓	-	-	-	-
Heyman et al.	1991	-	✓	-	-	-
Hall et al.	1992	-	-	-	✓	-
Perkins et al.	1997	✓	-	-	-	-
Fillenbaum et al.	1998	-	✓	-	-	-
Gurland et al.	1999	-	-	✓		-
Hall et al.	2001	-	-	-	✓	-
Tang et al.	2001	-	-	✓	-	-
Demirovic et al.	2003	✓	✓	-	-	-
Evans et al.	2003	-	-	-	-	-
Fitzpatrick et al.	2004	✓	-	-	-	-
Katz et al.	2012	-	-	-	-	✓

MMSE=Mini-Mental State Exam
SPMSQ=Short Portable Mental Status Questionnaire
CARE=Comprehensive Assessment and Referral Evaluation
CSI-D=Community Screening Interview For Dementia
MIS=Memory Impairment Screen

Table 3A: Final Syndromic and Etiologic Diagnostic Instruments

Study	Year	*DSM*	*NINDS-ADRDA*	*CA Criteria*	*ICD*	*HIS*
Folstein et al.	1991	✓	-	-	-	-
Heyman et al.	1991	✓	✓	-	-	-
Hall et al.	1992	✓	✓	-	✓	-
Perkins et al.	1997	✓	✓	-	-	✓
Fillenbaum et al.	1998	✓	✓	-	-	-
Gurland et al.	1999	✓	-	-	-	-
Hall et al.	2001	✓	✓	-	✓	-
Tang et al.	2001	-	✓	-	-	-
Demirovic et al.	2003	-	✓	-	-	-
Evans et al.	2003	-	✓	-	-	-
Fitzpatrick et al.	2004	✓	✓	✓	-	-
Katz et al.	2012	✓	✓	-	-	-

CA Criteria=California Criteria for Vascular Dementia
ICD=International Classification of Disease Versions 9-10 criteria for Vascular Dementia
HIS=Hachinski Ischemia Scale for Ischemic Vascular Dementia
DSM=Diagnostic and Statistical Manual of Mental Disorders Versions III-IV-R
NINDS-ADRDA=National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders

Table 4: Syndromic, Etiologic Criteria, Occurrence of Alzheimer's in African Americans

Study	Year	*Syndromic*	*Etiologic*	*Incidence*	*Prevalence*
Folstein et al.	1991	DSM III	-	-	4.0%
Heyman et al.	1991	DSM III	NINDS-ADRDA	-	16.0%**
Hall et al.	1992	DSM III-R	NINDS-ADRDA	-	5.5%
*Perkins et al.**	1997	DSM III-R	NINDS-ADRDA	1.2%**	4.8%**
*Fillenbaum et al.****	1998	DSM IV	NINDS-ADRDA	5.8%**	7.0%**
*Gurland et al.****	1999	DSM III-R	-	8.2%**	18.8%**
Hall et al.	2001	DSM III-R	NINDS-ADRDA	-	6.8%
Tang et al.	2001	-	NINDS-ADRDA	3.7%	-
*Demirovic et al.**	2003	-	NINDS-ADRDA	-	14.4%
*Evans et al.****	2003	-	NINDS-ADRDA	3.0%	-
Fitzpatrick et al.	2004	DSM IV	NINDS-ADRDA	15.7%	-
Katz et al.	2012	DSM IV	NINDS-ADRDA	3.5%	-

*male segment of cohort only; insufficient data to calculate rates for african american females
**dementia
***hybrid studies

Table 5: Incidence of Alzheimer's Disease in African American Populations

Study	Year	*Age*	*n*	*Follow-Up*	*Result*	*95% CI*
*Perkins et al.**	1997	> or = 50	682	-	1.6%	(0.5-2.4)
Fillenbaum et al.	1998	> or = 65	1775	3.0 years	5.8%	(2.6-9.0)
*Gurland et al.****	1999	> or = 65	729	1.5 years	8.2%	-
Tang et al.	2001	75.8 yrs**	610	7.0 years	3.7%	-
*Evans et al.****	2003	> or = 65	373	4.1 years	3.0%*****	(2.1-3.9)
Fitzpatrick et al.	2004	> or = 65	492	5.4 years	3.5%******	-
Katz et al.	2012	78.8 yrs**	350	3.9 years	3.3%	(2.2-4.9)

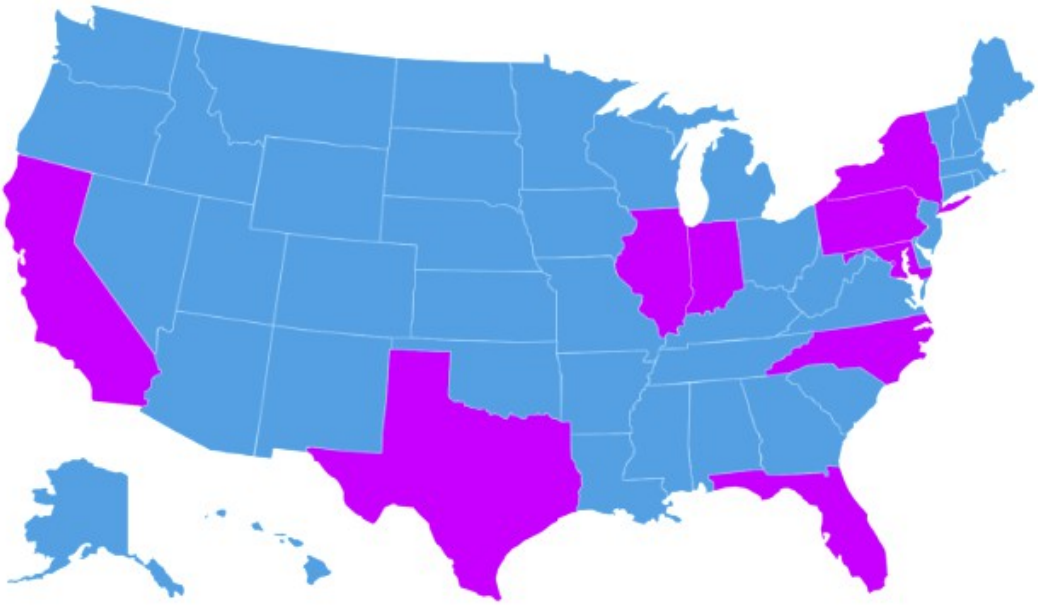
*male portion of cohort only; study authors: insufficient data to calculate female African American rates
**mean age of cohort
***hybrid sample populations, includes institutionalized study participants
****annual incidence
*****incidence rate per 1000 person years, age-adjusted

Table 6: Prevalence Proportions Of Alzheimer's Disease In African American Populations

Study	Year	*Age*	*n*	*Result*	*95% CI*
Folstein et al.	1990	> or = 65	210	4.0%	(1.6-SE)*
Heyman et al.	1991	> or = 65	83	16.0%	(7.9-24.1)
Hall et al.	1992	77.4 yrs***	2212	6.8%	(5.8-7.7)
*Perkins et al.***	1997	> or = 50	682	4.8%	(1.8-10.5)
*Fillenbaum et al.*****	1998	> or = 68	1175	7.0%	(2.1-11.9)
*Gurland et al.*****	1999	> or = 65	729	18.9%	-
Hall et al.	2001	76.8 yrs***	1892	7.5%	(4.3-10.6)
*Demirovic et al.***	2003	73.3 yrs***	289	14.4%	(10.3-18.5)

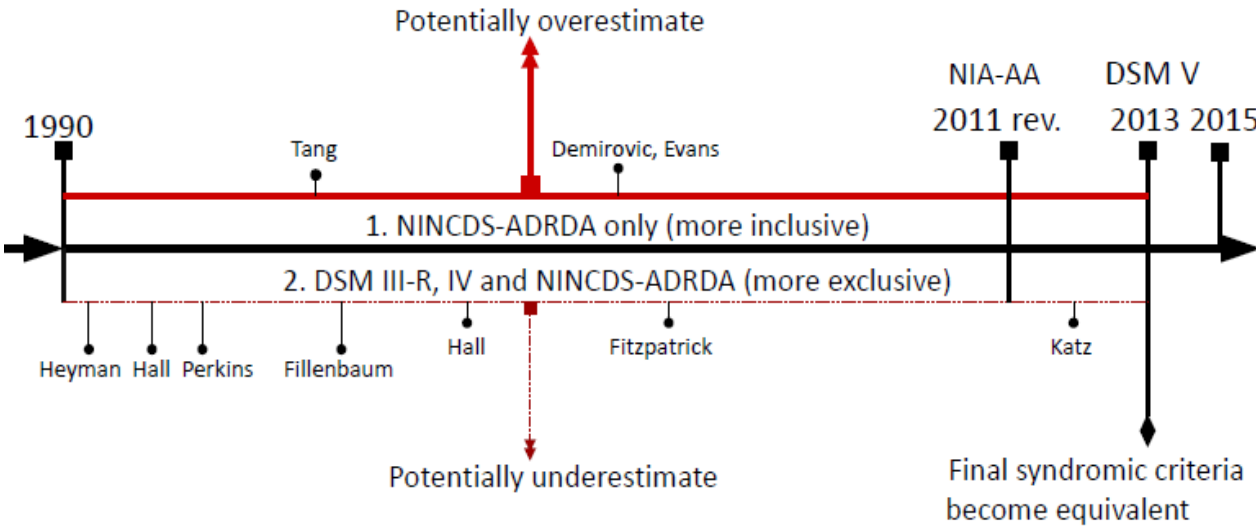
*SE=standard error
**male portion of cohort only; study authors: insufficient data to calculate female African American rates
***mean age of cohort
****hybrid sample population

Figure 1: Sampled Populations: African American Data Sources



Key: Purple=states study subjects were recruited from

Figure 2: Diagnostic Timeline: Final Syndromic and Etiologic Criteria



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