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Dementia in Africa: Current evidence, knowledge gaps and future directions

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AUTHORS' CONTRIBUTIONS

ROA conceptualized and developed the outline of the article. ROA, JY and AO researched the data for the article and wrote the first draft. RNK and AO reviewed and edited drafts of the article. All authors provided substantial intellectual inputs into, and revised drafts of the article and approved the final version of the article.

CONFLICTS OF INTEREST

All authors have no conflict of interest related to this article.

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Abstract

In tandem with the ever-increasing ageing population in low and middle-income countries, the burden of dementia is rising on the African continent. Dementia prevalence varies from 2.3 to 20.0% and incidence rates are 13.3 per 1000 person years with increasing mortality in parts of rapidly transforming Africa. Differences in nutrition, cardiovascular factors, co-morbidities, infections, mortality and detection likely contribute to lower incidence. Alzheimer's disease,

vascular dementia and HIV/AIDS associated neurocognitive disorders are the most common dementia subtypes. Comprehensive longitudinal studies with robust methodology and regional coverage would provide more reliable information. The apolipoprotein E (*APOE*) ε4 allele is most studied but has shown differential effects within African ancestry compared to Caucasian. More candidate gene and genome-wide association studies are needed to relate to dementia phenotypes. Validated culture-sensitive cognitive tools not influenced by education and language differences are critically needed for implementation across multidisciplinary groupings such as the proposed African dementia consortium.

Keywords

Africa; Dementia; Alzheimer's disease; Vascular dementia; Epidemiology; Genetics; Neuropathology. Biomarkers; Precision Medicine; Consortium

1. INTRODUCTION

Globally, Alzheimer's disease and other dementias constitute a major public health priority with substantial negative individual, social, and economic impacts.^{1,2} The current estimates from the World Health Organization (WHO) indicate that by 2050, 150 million persons, representing a 204% increase from 2017, will be living with dementia.^{3,4} Indications are that the majority of these increases will be found in low- and middle-income countries (LMIC) including within Africa.^{3–5} Worldwide, dementia is the 5th leading cause of death and the second leading contributor to death from neurological diseases.⁶ Recent estimates suggest that over 818 billion USD is spent annually on dementia related care worldwide and by 2028 the worldwide cost of dementia care is estimated to be >2 trillion USD.⁷ These include direct medical and other formal and informal health and social care costs.

The projection that over 68% of persons with dementia will reside in LMICs by 2050⁵ is largely due to the demographic transition and population growth in the LMICs including certain African countries, which are amongst the world's most populous. The burden of dementia is shared by the person, their immediate family, caregivers, and the health, social, legal, and financial systems of the community at large. In Africa, as in many other underserved populations, additional strains on dementia care exist, attributable to globalisation, rapid socio-economic transitions, and the gradual erosion of key informal care systems such as multigenerational family structures which are the bedrock of dementia care.⁸ As such, the continent needs to devise robust alternate plans for the care of persons with dementia within the formal healthcare sector, taking advantage of global advancements in preventive, therapeutic and rehabilitative care of the condition.

Currently, there is a dearth of information on the basic and translational science of dementia in Africa. There is paucity of neuroimaging and fluid biomarker studies, and very few neuropathological and genomic studies limited to candidate gene reports in pockets of cohorts. Basic and clinical research in Alzheimer's disease and other dementias are also constrained in countries with greater public awareness and affluence. There is therefore a limitation in the capacity for rigorous endophenotyping and the delivery of evidence-based personalized/precision approaches to dementia care, especially in the context of the unique

diversity of African genomes and their interactions with the local environment. This review aims to summarize the current epidemiological evidence on dementia in Africa, highlight challenges, identify knowledge gaps, and suggest future research directions and goals.

2. CURRENT EVIDENCE

2.1. Epidemiology

More than two-thirds of the world's population of older people (≥ 65 years old) reside in less developed countries, many of whom are in Africa.⁹ The prevalence and incidence of dementia increase with age.¹⁰ However, despite the projected large increases in the number of persons living with dementia, current estimates of prevalence and incidence of dementia from multiple studies in Africa are among the lowest in the world. While this may be due to numerous factors including low life expectancy in many African nations, it is however to be noted that dementia data derived from observational studies using similar methodological approaches and designed to reflect the diversity of Africa are still relatively few even though growing. The paucity of data is a reflection of the challenges of conducting quality research in many resource poor African countries. (Figure 1)

2.2. Incidence

Information on the incidence of dementia in Africa is currently sparse (Figure 1). There are four recent reports on dementia incidence from Western Africa, and one each from Central Africa and Northern Africa respectively. Notably, most of the data on incidence are from one country, Nigeria. Current incidence estimates from Sub-Saharan Africa (SSA) are similar to that for other low- and middle- income countries at 13.26/1 000 person years implying 367 698 new cases each year.¹¹ The Alzheimer's Disease International (ADI) meta-analysis shows that incidence doubles for every 7.7 year increase in age in sub-Saharan Africa (SSA).¹¹ For Northern Africa, a recent review on the epidemiology of dementia in the Middle East and North Africa (MENA) estimated a crude incidence of 27/1,000 over a 20-year period for Egypt.¹² Similar to prevalence, the reported annual incidence rates of dementia in Africa are generally lower than rates reported among populations of older persons living in Europe and North America.¹³ Differences in diet and burden of cardiovascular risk factors, medical co-morbidities, access to quality health care and mortality have been suggested as possible reasons for the lower incidence of dementia in Africa compared to higher income regions of the world.¹⁴ In one study comparing the incidence of dementia and Alzheimer's disease in two comparative cohorts of African Americans and Yoruba Nigerians aged 70 years or over and evaluated a decade apart in 1992 and 2001 respectively, the standardised annual incidence rates of dementia and AD were relatively stable in the Yoruba African cohort (dementia: 1.7% vs 1.4%; AD: 1.5% vs 1.0%) whereas there was a significant decline among the African Americans (dementia: 3.6% vs 1.4%; AD: 2.5% vs 1.3%).¹⁵

2.3. Prevalence

Studies in Africa have generally reported varied but generally lower prevalence of dementia compared with findings in Europe and America.¹⁶ Limitations with many African studies include low quality of methods used, types of study settings (i.e. in-patients, outpatients,

nursing homes, autopsy), and limited coverage of the different African regions.¹⁷(Table 1). The pattern of the findings is such that hospital-based studies report the lowest prevalence estimates of dementia in Africa.¹⁷ However, 48% of a sample of nursing home residents in Nigeria met the clinical diagnostic criteria for dementia.¹⁸

As highlighted in a systematic review by Mavrodaris et al, variation in dementia prevalence depends on the criteria used and methodology employed.¹⁹ Overall, higher prevalence estimates of up to 20.0% have been reported in community-based studies using different approaches and multiple rating scales for defining dementia.^{20,21,30} There are also important geographical variations in the prevalence estimates of dementia. The lowest prevalence rate of 2.3% has been reported from Ibadan, Nigeria²² and Al Kharga in Egypt.²³ The reported prevalence of dementia appears low in Western Africa with most studies reporting prevalence around 3%^{24–26} and much lower than figures above 6% in Central, Eastern, and Southern Africa.^{21,27–30} Figures from Northern Africa tend to be intermediate and range from 2.3% to 5.1%.^{23,31–34} (Figure 2; Table 1)

2.4. Mortality

The recent report on dementia in SSA published by ADI included results from four African studies that have estimated dementia mortality risk. The result showed an increased mortality risk with an hazard ratio ranging from HR=1.5 (95%CI: 1.2–1.8)³⁵ to HR=6.3 (95%CI: 3.2–12.6)³⁶ and an estimate from meta-analysis of HR=2.3 (95%CI: 1.0–3.5).¹¹ Contrary to expectations of a higher risk of dying from dementia in the developing compared to developed countries, some studies in Africa reported a lower risk of mortality from dementia than has been reported in several middle- and high-income countries.³⁵ Urban dwelling and anthropometric evidence of under-nutrition were independent predictors of dementia mortality in the Ibadan Study on Ageing cohort.³⁵

2.5. Economic cost

Data on the direct costs of dementia in Africa are largely non-existent. However, it has been estimated that the cost of dementia in 2015 represented 6.2 billion US dollars for SSA, of which 70% is attributable to the cost of informal care most often provided by relatives and families of people living with dementia (Guerchet et al., 2017).¹¹ A limit of this estimate is that it is based on imputations using the countries' Gross Domestic Product and the medical/social/informal cost distribution from a multicentric study in LMICs from the 10/66 Dementia Research Group. There is a lack of original data regarding health service utilization and cost of services in African countries, which could inform a better and more precise estimation of the cost of dementia in the region.³⁷

2.6. Risk factors

A number of known risk factors for dementia have been evaluated by various studies in Africa. While the results do not significantly differ from those reported in other regions, the strength of the evidence is limited by the fact that most of these studies were cross-sectional in design. New risk factors for dementia such as air and environmental pollution need further study in Africa. Hence, more longitudinal studies that can inform context-specific interventions are needed from multiple African regions.

2.6.1. Non-modifiable Risks

2.6.1.1. Age and sex: Age is the most consistent non-modifiable risk factor for cognitive impairment and dementia. Various studies have corroborated the known association with both prevalent and incident dementia in the African context.^{11,12,21,22,38–41} Regarding association with sex, many studies have also reported that dementia and AD are either more prevalent in the female sex,^{22,24–26,29} or the male sex⁴² or have found no association²¹. The association with the female sex may be linked to a higher life expectancy and often poorer education.

2.6.1.2. Genetic factors: Using mainly candidate gene approaches, some genetic loci/alleles have been associated with dementia phenotypes in Africa, with the apolipoprotein E (*APOE*) gene being the most studied (Table 2). Whereas the *APOE* $\epsilon 2$ allele is protective,⁴³ the *APOE* $\epsilon 4$ allele increases the risk of AD in Caucasians⁴⁴ but not conclusively in indigenous African populations (particularly those in SSA). Older population-based studies showed weak or no association between *APOE* $\epsilon 4$ and cognitive decline²⁴ or AD^{24,45–47} whereas more recent data reported a significant association between *APOE* $\epsilon 4$ homozygosity⁴⁸ and incident AD among Yoruba Nigerians.⁴⁹ It is particularly intriguing that whereas *APOE* $\epsilon 4$ allele has been clearly associated with AD in Northern Africa, the association has been non-existent or rather weak in SSA.⁵⁰ While gene – environment interactions might influence the link, there is also the plausibility of the existence of novel genetic variants that have stronger genetic contribution to AD biology in SSA populations.^{8,51} Further studies are therefore needed to explore the geographical disparities in the relative association of the *APOE* alleles and AD in different African regions, although ancestry-specific genetic factors near *APOE* have been implicated.⁵² The *APOE* $\epsilon 4$ allele has also been linked with mortality⁵³ and white matter integrity in adults with HIVinfection.⁵⁴ Studies from Northern Africa have reported other genetic associations of AD with mutations in the Amyloid Precursor Protein (*APP*), Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) genes.^{55,56} In South Africa, *PSEN1* mutation has been reported in a family with early onset AD⁵⁷ and the *CHMP2B* polymorphisms in a South African family with frontotemporal dementia (FTD).⁵⁸ Newer studies have also reported associations of *ACEI* and *PONI-L55MT* alleles, *GTICC* haplotype and increased dementia risk, whereas *AADTT* reduced dementia risk by 80%.⁴⁸ Landoulsi *et al.* reported no major association of *TREM2* gene with late-onset AD in a Tunisian cohort⁵⁹ but plasminogen activator inhibitor 1 (*PAI-1*) 4G/5G polymorphism demonstrated increased risk of dementia.⁶⁰ Considering the great genetic diversity on the African continent, it is probable that unique genetic variants at previously identified loci and novel loci associated with both the risk of and protection from AD and related dementias remain to be discovered.

2.6.2. Modifiable Risks

2.6.2.1. Cardiovascular risk factors: Several studies have demonstrated associations between traditional cardiovascular risk factors – hypertension,^{61,62} type 2 diabetes,^{26,63} dyslipidaemia,⁶⁴ and peripheral arterial disease^{65,66} and cognitive impairment - and dementia phenotypes.⁶⁷ While peripheral arterial disease and systemic hypertension were linked to prevalent dementia in Central and West Africa, respectively¹⁷, high total cholesterol and low-density lipoprotein were predictors of incident dementia in Nigeria.⁶⁴

Mild cognitive impairment (MCI) is a precursor of dementia. In one community-based study from Lalupon, southern Nigeria, MCI was associated with mean arterial pressure (MAP) and pulse pressure⁶⁸ while a Ugandan community-based study found an association between cognitive impairment and carotid artery plaques.⁶⁹ Hypertension and type 2 diabetes were also found to be associated co-morbidities in Nigerian hospital-based dementia cohorts.^{70–72} Other less established risk factors have also been shown to increase the risk of dementia in Africa include homocysteine,⁷³ and folate.⁷⁴

2.6.2.2. Literacy and education: As shown in the extant dementia literature particularly from the West, studies from Africa have also demonstrated an association between low educational attainment and increased dementia risk.^{41,65,75} Based on the cognitive reserve hypothesis,^{76–78} it is suggested that education might interfere with the phenotypic expression of dementia. However, other studies have reported a lack of association between education and dementia on the continent^{22,29,79,80}. Nonetheless, it is noted that the majority of older Africans included in these studies had no formal education lasting 7 years and only a minority had a few years of formal education. It is likely that this low level of formal education may not be an appropriate signature of cognitive reserve. Indeed, many older Africans even centenarians despite having no formal Western education play key social roles and have communal responsibilities that better reflect their cognitive ability and likely plays a role in maintaining cognitive reserve. Clearly, traditional systems of learning which can also improve cognitive abilities need to be considered. As such, one has to consider the limitations and appropriateness of directly translated cognitive scales that have been used in the past in interpreting the association. Fortunately, newer context-sensitive tools are being developed for better cognitive evaluation in the region to address these observations.^{81–83}

2.6.2.3. Lifestyle factors and social isolation: A review of the literature from Africa demonstrates limited evidence on the relationship between lifestyle factors such as diet, physical activity, smoking and alcohol and cognitive impairment and dementia. Anthropometric markers of malnutrition such as reduced body mass index,^{65,84} low arm muscular circumference, low mid-upper arm circumference^{84–86} and lower consumption of oily foods have been associated with dementia.⁸⁵ Undernutrition, especially with low consumption of oleaginous diet was associated with prevalent dementia in a study involving two countries from Central Africa^{17,85} while a history of smoking, current smoking, and weight loss were linked to incident dementia in Nigeria.⁸⁴ Pre-stroke daily fish intake was found to be protective against cognitive impairment among stroke survivors.⁴¹ It has also been suggested that the lower risk of dementia among Yoruba Nigerians is related to low levels of saturated fat and high fiber content in their traditional diet which consists of yam tubers (*Dioscorea rotundata*), grains, vegetables, and fish.⁶⁴ Fiber has many beneficial effects, including alteration of the gut microbiota and consequent implication for the gut-brain axis and related brain disorders. Based on data from the WHO's Study on Global AGEing and Adult Health (SAGE), a cross-sectional, community-based study conducted in South Africa demonstrated an association between food insecurity and cognitive impairment.⁸⁷ However, findings from the two studies on the link between alcohol and dementia were contradictory.^{85,88} The importance of lifestyle and environmental factors and their interaction with genetic factors has been elucidated in comparative cross-national

studies.⁸⁹ The care structure for older persons in traditional African societies provides a rich social support network with older persons often living in multigenerational settings, although this is now been eroded by migration, urbanization and globalization.⁹⁰ The effect of these changes in care structure on the trends of cognitive impairment and dementia in Africa deserve further research focus. Available data, however, showed that living with others was protective against dementia in the Ibadan cohort of the Ibadan – Indianapolis Dementia Project⁹¹ while low social network⁹² and poor social engagement³⁸ were risk factors for prevalent and incident dementia in a Senegalese and another Nigerian study respectively. The role of sleep, hearing loss, head trauma, air pollution and environmental toxins such as lead have not been studied as potential risk factors for dementia in the African context.

2.6.2.4. In utero and early life factors: The role of in – utero and early life exposure in dementia occurrence has been the focus of several studies in high income countries,^{93,94} but these have not been widely explored in Africa. Well-designed longitudinal studies to explore the role of early life factors will require considerable funding and expertise. Pilleron *et al*, however, reported a significant association between the death of one parent during childhood and dementia in late life from studies conducted in the Central African region.⁹⁵

2.6.2.5. HIV and Other Infections: Substantial evidence abounds demonstrating HIV as a cause of neurocognitive disorders with about two-thirds of people living with HIV diagnosed with probable HIV associated neurocognitive disorder (HAND).^{96–102} With over 11.3 million HIV/AIDS patients affected by HAND⁹⁸, it has been suggested that the burden of HAND in Africa is likely to rank among the highest of any region in the world. There are several reasons for the high burden of HAND on the continent. First, Africa has the highest HIV/AIDS burden in the world. Secondly, in many parts of Africa late presentation of HIV is rife with relatively advanced infection characterized by severe immunosuppression, which directly predisposes to HAND.^{101,103} HIV also increases the risk of atherosclerotic strokes¹⁰⁴ and of tuberculosis including tuberculous meningitis and tuberculomas that indirectly increase risk of cognitive decline and dementia. Furthermore, the development of new genetic recombinant forms of HIV1 as well as its genetic variation in patients with HAND as reported from Cameroon,^{105,106} pose additional challenges to reduction of the HAND burden and vaccination research. When feasible, including HIV screening in the future generations of population-based studies of dementia could fill some knowledge gap.

The role of toxoplasmosis infection in dementia emphasizes the fact that parasitic infectious agents might be particularly important contributors to cognitive impairment and dementia in Africa.¹⁰⁷ A recent case-control study reported a higher prevalence of cognitive impairment in people with epilepsy, particularly decreased executive function and verbal fluency, than in people without epilepsy in an onchocerciasis-endemic area of Cameroon.¹⁰⁸ Evidence from children with retinopathy-positive cerebral malaria suggests some cognitive impairment^{109,110} Longitudinal studies are necessary to delineate the role of parasitic diseases in cognitive function and dementia in Africa.

2.7. Dementia subtypes in Africa

Alzheimer disease (AD) and vascular cognitive impairment and dementia (VCID) remain the most commonly reported dementia phenotypes (Table 1).³⁷ A report from the Ibadan-Indianapolis dementia study suggests that in a densely populated urban community in Ibadan, south-Western Nigeria, only 12% of all new cases of dementia between 1995 and 2001 received a diagnosis of vascular dementia based on DSM III-R and ICD 10 criteria.¹³ In a recent systematic review, the proportion of VCID in multiple African studies ranged between 17 and 41% for all phenotypes of dementia depending on the type of study sample.¹¹¹ Other dementia phenotypes reported in Africa include frontotemporal dementia,¹¹² dementia with Lewy bodies,¹¹³ Parkinson's disease dementia,⁷¹ and cognitive impairment or dementia associated with Creutzfeldt-Jakob disease,¹¹⁴ Huntington disease^{115,116} and sickle cell disease (SCD).^{117–121} However, confirmation of dementia subtypes is only definitive following post-mortem neuropathologic examination and this level of diagnostic certainty has not been achieved in existing studies from Africa^{122,123} with the exception of the first reported case of dementia with Lewy bodies¹¹³. SCD is well known to predispose to vascular brain injury, particularly silent cerebral infarction (SCI), which are often associated with cognitive impairment.¹²¹ Studies in Cameroon and Nigeria have revealed that executive function in particular, attention and working memory are severely affected in SCD children with high cerebral blood flow velocities.^{118–120} A recent comparative magnetic resonance imaging (MRI) study in Tanzania showed that SCI, vasculopathy, and hemoglobin are independent risk factors for diffuse white matter injury in children with SCD.¹¹⁷

2.8. Living with dementia in Africa

A common problem in Africa and probably other LMICs for persons living with dementia is grappling with stigmatization. Limited studies have reported that stigmatization is rooted in belief systems, commonly cultural¹²⁴ or supernatural,¹²⁵ where persons with dementia are thought to be witches. Even though the role of traditional healers, community leaders and faith healers in health promotion cannot be overlooked, there is nevertheless evidence that these community opinion leaders commonly do not view dementia as a specific disease but rather a feature of normal ageing.^{126–128} Occasionally, carers and even healthcare workers hold similar belief, an observation that suggests a need for education of both the general population and healthcare workers.^{125,129} There is evidence in support of higher educational attainment being associated with less stigmatising attitudes.¹²⁵ The need for education is particularly key as caregivers are unlikely to seek health interventions without adequate information. In Nigeria about a third of people feel that even individuals living with dementia would prefer not to know or let others know their disease status.¹³⁰

To relieve caregiver burden, formal home care is a viable option in high-income countries but not in Africa. Negative attitudes to formal care exist among some family members and in some society irrespective of economic status, and religious beliefs contributing to the perspective.¹³¹ A study in South Africa showed that less than a third of respondents were willing to pay for formal home caregivers, with higher education, female sex and older age associated with willingness to pay.¹³² The challenges of formal care setting include the risk of delirium associated with dementia due to infective causes.^{133,134} However, there

are also limitations with formal care, among which is sub-optimal clinical practices among healthcare workers. A qualitative study carried out in Southwestern Uganda noted that healthcare staff did not have adequate specific mental health training for assessment and diagnosis of dementia. Healthcare workers with some specialized training in mental health were more likely to use neuropsychological tests and brain imaging in the diagnosis of dementia.¹³⁵

2.9. Treatment options

2.9.1. Pharmacological: While there are no approved disease-modifying medications for most of the primary dementias, a few strategies such as immunotherapy directed against amyloid and/or tau, and inhibition of amyloid synthesis are currently in advanced stages of development.^{136–138} There are reports on the potential use of medicinal plants.^{139,140} However, the current treatment approaches are directed at symptom relief, with options including adjustment of neurotransmitters (acetylcholine, norepinephrine, and serotonin), behavioural modification, and treatment of medical complications. Access to and affordability of pharmacological agents for symptomatic management remains a significant challenge in Africa. It is also necessary to enlist common relevant medications on the WHO essential drug list. Traditional approaches to the treatment of dementia in Africa are often influenced by the belief about the origin of the ailment or the trajectory including trial of medicinal products and hospital care. African family and/or caregivers of individuals with dementia often consider the use of herbal or folk remedies and reports on the potential efficacy of some local African medicinal products are emerging^{139,140} However, when anticipated improvement in memory, functioning or quality of life is not achieved, alternative and informal care approaches are often resorted to.

2.9.2. Non-pharmacological: Non-pharmacological approaches are important in the management of dementia worldwide and probably more so in Africa. Generally healthcare staff and home care workers prefer interpersonal approaches above medication to manage distressing behavioural disorders, except in certain situations.¹⁴¹ Non-pharmacological interventions aimed at reducing disabilities consist of patient education, cognitive interventions, and lifestyle modifications.¹⁴² Cognitive stimulation therapy has been studied in Nigeria and Tanzania with reported clinical benefits including substantial improvements in cognition, anxiety and other behavioural symptoms.^{143–145}

3. GAPS AND FUTURE DIRECTIONS

3.1. Cognitive evaluation in Africa

Robust cognitive tools that are culture-sensitive with excellent psychometric properties and resistant to the differences due to effects of education and languages are needed for deployment across multiple regions of Africa. The need to utilize cognitive and functional assessment instruments that are culturally appropriate and adopt common approaches to clinical evaluation of dementia across African countries cannot be over-emphasized. This is because comparison of dementia rates from different studies may be fraught with difficulties due to variations in assessment tools and approaches. Various investigators have tried to improve on neuropsychological tests used on the continent with a view to adjusting

for the peculiarities of the environment, ease of administration and educational status. The Community Screening Instrument for Dementia (CSI-D) is a screening tool that was developed for settings with low education.^{146,147} It has been deployed in several dementia epidemiological studies in sub-Saharan Africa and the 10/66 dementia research group has developed a shorter version of it with excellent psychometric properties.¹⁴⁸ The Rowland Universal Dementia Assessment Scale (RUDAS) has been validated for dementia screening in Arabic-speaking population.¹⁴⁹ The Intervention for Dementia in Elderly Africans (IDEA) Cognitive Screen⁸³ is a six-item instrument that was more recently developed with components derived from the CSI-D (items 1–4). Item 5 was taken from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word recall test, while the sixth item was designed to measure praxis and consists of a matchstick design test originally developed by Baiyewu *et al.*¹⁵⁰ The IDEA Cognitive Screen therefore includes measures of delayed recall, orientation, two measures of executive function, verbal fluency and abstract reasoning, praxis and long-term memory. No items were included requiring reading, writing, drawing or calculation in order to reduce possible educational bias.^{81,82} It has been validated in Nigeria (Yoruba language) and Tanzania (Swahili language) with excellent psychometric properties including the Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.99 in Nigeria and 0.91 in Tanzania.^{81,83} Cut off score is <7 for possible dementia. The IDEA cognitive screen was used to conduct a dementia prevalence study in Lalupon near Ibadan, Nigeria and obtained rates that were largely similar to previous rates obtained (using the CSI-D) in the Ibadan -Indianapolis Dementia Project.⁴² The International HIV Dementia Scale which was developed in Uganda has been used as a screening tool for HAND in several African countries.^{151,152}

The next important step for promoting reliable cognitive evaluation in Africa is the development of normative data across the lifespan, based on the validated culturally - sensitive neuropsychological test batteries and screening instruments. Examples of normative data have been reported from Cameroon in the paediatric and adult populations.^{99,153}

For functional assessment, the Clinician Home-based Interview to assess Function (CHIF) was developed and validated by the Indianapolis-Ibadan dementia research group.¹⁵⁴ The IDEA study Instrumental Activities of Daily Living (IDEA – IADL) was also recently developed and validated among rural dwelling Tanzanians. It had an AUROC of 0.896 for DSM -IV dementia and 0.937 when used in conjunction with the IDEA Cognitive Screen, with no bias for age, sex or education.¹⁵⁵ A shorter version, the 3-item IDEA-IADL questionnaire has also been validated for evaluation of instrumental activities of daily living.¹⁵⁶ The Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog) has been adapted for low literacy and has good psychometric properties.¹⁵⁷ The IDEA - IADL App-Based Cognitive Screening instrument mobile application has now been developed and validated among non-specialist rural community workers. The AUROC was 0.78 with good sensitivity and fair specificity.¹⁵⁸ In Central Africa, the Central African Daily Interference Scale (CA-DFI), a 10-item scale, has also been developed with psychometric properties supporting the reliability and internal validity of the CA-DFI scale as a promising tool for functional assessment in the elderly for the diagnosis of dementia in Central Africa.¹⁵⁹

3.2. Tracking epidemiological trends

African populations are aging rapidly such that by the year 2050, 212 million older persons 60 years of age and older will be residing on the continent in keeping with trends in other LMICs.¹⁶⁰ Concomitant with this is a projected increase in the prevalence of aging – associated disorders of the brain such as Alzheimer’s and Parkinson’s diseases. Hence, more epidemiological studies are needed in Africa that will accurately track the secular trends of cognitive impairment and dementia and dementia subtypes in Africa. Community-based studies in Tanzania have reported worsening cognitive decline over 2 years of follow-up¹⁶¹ and increased prevalence of dementia from 6.4% to 8.9% in a rural cohort of older persons > 70 years over a 9-year interval and using the same methods of cognitive assessment.¹⁶² This is in contrast to declining trends of dementia reported in high-income countries. Over the years, there has been improvement in dementia epidemiological studies and results suggest an increasing prevalence.¹¹ Increasing prevalence may also suggest greater awareness of dementia in Africa. Other potential, but less studied sources of variation in prevalence estimates of dementia in Africa include genetic predisposition, lifestyle factors, urban versus rural distribution of study participants, differences in literacy levels and changes in the age structure of the studied population. Tracking epidemiologic trends provides relevant data needed to inform identification of specific modifiable risk factors for cognitive impairment and dementia that can inform the development of culturally appropriate interventions and the formulation of elderly-friendly policies in African countries.^{11,161}

3.3. Insights from neuropathologic evaluation

Accurate phenotyping of dementia subtypes depends on neuropathologic techniques as the gold standard. Although Alzheimer’s disease is typically characterised by the presence of amyloid plaques and neurofibrillary tangles, concomitant vascular and/or neurodegenerative pathologies are often detected and produce mixed phenotypes. For example, in a community-based autopsy cohort, approximately 60% of patients with clinical diagnoses of Alzheimer’s-type disease were in fact affected by vascular disease pathology, TDP - 43, or Lewy body pathology rather than plaques and tangles.¹⁶³ Clinicopathological studies are therefore critical in shaping our understanding of the aetiology, natural history and mechanisms of disease and to help in formulating the frameworks necessary for the discovery of new therapeutic and preventative interventions.¹²³

In Africa, a post-mortem study of brain tissue of neurologically normal Nigerian Africans showed incidental Lewy body pathology burden similar to figures that were then reported among individuals of European ancestry from the UK and USA.¹⁶⁴ The significance of this finding was the suggestion that the correspondence of the frequency of Parkinsonian pre-symptomatic neuropathology (and indirectly the risk of Parkinson’s disease) in Nigerian Africans and Caucasians in the UK and USA might indicate similarity in the predisposition to Parkinson’s disease, while the disparity in prevalence (lower in Nigerian Africans) might be attributable to lower life expectancy in the latter.¹⁶⁵ This also implies that as African populations age, the prevalence of PD and PD dementia might rise in parallel. However, in an autopsy survey of 198 brains of Nigerians aged 40 years and above (including 45 individuals (23%) who were above 65 years of age) to determine the occurrence of pathological hallmarks of AD, findings showed mild cortical neuronal loss and absence of

neurofibrillary tangles, senile plaques and amyloid angiopathy – characteristic pathological features hallmarks of AD.¹⁶⁶ Clinically at that time, dementia was rather rare.¹⁶⁷ A similar post-mortem study on non-demented elderly East Africans reported significant neocortical amyloid beta deposits and tau protein reactive neurofibrillary tangles evident in the hippocampus in 15.2% and 12.5% of the subjects respectively similar to findings in age-matched elderly Caucasian control subjects from Cleveland, USA.¹⁶⁸

Other studies involving multiracial populations of North America have reported racial disparities in the epidemiology and neuropathology of cognitive impairment and dementia. In a report from the Rush Study, African American subjects were less likely to have Alzheimer pathology as a single dementia pathology compared to Caucasian subjects (19.5% vs 42.0%), but were more likely to have Alzheimer pathology mixed with an additional pathology (70.7% vs 50.6%) particularly Alzheimer pathology and Lewy bodies, and Alzheimer pathology, Lewy bodies, and infarcts. Furthermore, black subjects also had more severe arteriolar sclerosis and atherosclerosis.¹⁶⁹ Similarly, a recent multiracial Brazilian neuropathological study showed a comparable reduction in AD pathology but higher vascular pathology in the brains of subjects of African ancestry.¹⁷⁰

3.4. Unravelling the genetic architecture

The observations reported above beg the question of whether there is a protective gene at play that mitigates the amyloid depositing effect of *APOE ε4* in African ancestry populations. This lack of clarity is due to the fact that little is yet known about the genetic architecture of AD among indigenous Africans and there is inconsistency in the reported association of AD with *APOE-ε4* allele among Africans.^{8,46,49,50} Even though Africa is the origin of modern humans and harbors the greatest genetic diversity in global populations only a fraction of the genetic diversity among Africans has been surveyed with < 2% of genome wide association studies (GWAS) comprising African data.¹⁷¹ In a recent high-depth study of African genomes aimed at further exploration of African genomic diversity, whole-genome sequencing analyses were performed on 426 individuals from 50 ethnolinguistic groups under the aegis of the Human Health and Heredity in Africa (H3Africa) Consortium. The study found more than 3 million previously undescribed genetic variants.¹⁷² The implications of these observations are enormous for understanding the genetic basis of cognitive impairment and dementia in African ancestry and global populations. Thus, greater representation of indigenous Africans in dementia genomic research including GWAS and whole exome or whole genome sequencing approaches will enhance diversity and inclusiveness and enable novel insights into the biology of brain ageing, cognition, AD and other phenotypes. In addition, fine mapping of loci and variants already described will be enhanced to pinpoint precise causal genetic variants.¹⁷³ Furthermore, such studies will facilitate translational genomics, development of Afrocentric polygenic risk scores, unravel new pathways, biomarkers and drug targets for the enhancement of precision/ personalized dementia care. It will also improve our understanding of disparities in dementia phenotypes, risk factors and outcomes.^{123,174,175} Furthermore, such efforts will be in consonance with the US National Dementia Plan to prevent and effectively treat AD and AD - related dementias (ADRDs) by 2025¹ and the

National Academy of Medicine recommendation to utilize global health research to benefit Americans and global populations.¹⁷⁶

3.5. Fluid, neuroimaging and other biomarkers

Of all the causes of primary dementia worldwide, AD and VCID account for 70 – 80%, the other major causes being frontotemporal dementia, Parkinson's disease dementia and Lewy body dementia.¹⁴² All primary dementias except VCID are due to neurodegenerative proteinopathies— misfolded protein form inclusion bodies that are toxic to the neurones and implicated in neuroinflammation, glial reaction and neurodegeneration. Amyloid beta (AD), tau protein (AD, fronto-temporal lobar degeneration, cortico-basal degeneration, and progressive supra-nuclear palsy), TAR DNA-binding protein 43 (TDP-43) (fronto-temporal lobar degeneration(FTLD), RNA- binding Fused in Sarcoma (FUS) (FTLD), and alpha-synuclein (Parkinson's disease dementia, Lewy body dementia) are the main proteins elucidated and the neuropathological process initiation often precedes the recognizable clinical expression of disease by several years.¹⁴²

Recent studies have highlighted the role of biomarkers – to predict the likelihood of progression to dementia from MCI (cerebral amyloid angiopathy, mesial temporal lobe atrophy on MRI), to confirm clinical diagnosis, and standardize clinical research as clearly captured in the recent National Institute of Aging – Alzheimer's Association (NIA-AA) AD Diagnostic Criteria.¹⁷⁴ There are major advances in imaging and fluid biomarkers particularly in AD neurobiology. Cerebrospinal fluid (CSF) biomarkers including amyloid beta 1–42, phosphorylated (p-tau)181 and total (t-tau) tau are of diagnostic significance. CSF Aβ1–42 and positron emission tomography (PET) amyloid imaging with Pittsburgh Compound B are markers of brain beta amyloid deposition, whereas increased levels of CSF total (t-tau) and phosphorylated (p-tau) tau, hypometabolism on fluoro - deoxyglucose PET scan and atrophy on structural MRI scan are markers of neurodegeneration.^{142,175} And more recent data have revealed the utility of blood p – tau181 as a potential diagnostic marker.^{177,178}

A recent meta-analysis found that cerebrospinal fluid t-tau and p-tau 181 were consistently lower in African American than Caucasian individuals, in samples with normal cognition or with mild cognitive impairment/dementia.¹⁷⁹ This suggests that racial differences should be taken into consideration in interpreting differences in biomarker levels in the dementia phenotypes among individuals of different ancestries. For the other dementia phenotypes, there are also useful neuroimaging modalities including MRI and FDG-PET, tau-PET for FTLD, dopamine transport scan for LBD/PDD, and diffusion tensor imaging for VaD.¹⁴² SPECT studies are desirable for differentiating dementia subtypes particularly where PET may not be available and use of Pittsburgh Compound B for in-vivo imaging of amyloid may be difficult.¹⁸⁰

In Africa, there are limited datasets on imaging and fluid biomarkers. Africa lags behind in these advances due to lack of investments in relevant research infrastructure and expertise and the high cost of these advanced modalities. Nevertheless, there is a ray of hope in the horizon as efforts are beginning to yield fruits. Global brain atrophy and medial temporal lobe atrophy on MRI were significantly associated with cognitive impairment in a cohort of

Nigerian stroke survivors¹⁸¹ while MRI - determined thinning of the corpus callosum was associated with central nervous system disease severity and reduced immunity in a cohort of South African children living with HIV.¹⁸² Other studies have evaluated the role of CSF-based biomarkers,¹⁸³ and peripheral blood cell biomarkers in HIV-associated neurocognitive disorders.⁹⁷ Muscle strength measured using handgrip strength has been considered as a biomarker of mild cognitive impairment in LMICs.¹⁸⁴

3.6. Integrative transomics and precision medicine for dementia

Emerging insights from progress in multi - omics research suggest that dysregulation of molecular pathways at multiple levels including the genome, epigenome, transcriptome, proteome and the metabolome in response to numerous risk factors and triggers are involved in the neuropathological cascades that ultimately result in cognitive impairment and dementia.^{185,186} Thus, an integrative approach involving the exploration of sociodemographic, lifestyles, clinical, imaging, genetic, epigenetic, fluid biomarkers and pathologic substrates of cognitive decline and dementia in diverse populations including indigenous Africans will provide useful insights into new pathways, processes and networks, potential identification and characterization of novel biomarkers for prevention, risk profiling, early detection, diagnosis, prognosis and treatment of cognitive disorders in a precision medicine framework.^{187,188}

4. COVID- 19 AND DEMENTIA IN AFRICA

The corona virus disease 2019 (COVID - 19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a pandemic of current global proportions and importance.¹⁸⁹ It is generally known that individuals living with cognitive impairment and dementia are particularly susceptible to the viral infection because of their age, co-existing morbidities, immune senescence and reduced ability to adhere to the preventive protocols.^{190,191} In Africa, there have been >2.7 million COVID-19 cases and long term consequences are of particular concern (www.afro.who.int). Mortality rates are also very high in this population even though African data are sparse.^{192,193} The peculiar challenges of COVID - 19 and the elderly in Africa are premised on further erosion of the social support structure by social distancing, weak and fragile healthcare systems, worsening poverty and poor healthcare financing.^{191–193} The situation is further aggravated by the dependence on carers and caregivers for the performance of activities of daily living. This is fraught with the risk of infection with COVID –19 of both the person living with dementia as well as the caregiver. Social distancing also predisposed to exacerbations of neuropsychiatric symptoms like anxiety, agitation and depression.¹⁹⁴ To mitigate these challenges in the African context, social connection and interactions needs to be maintained with older adults, persons living with dementia and their carers inspite of ‘spatial distancing’. Family members and healthcare providers can keep in touch through various digital technologies including video and audio phone calls, WhatsApp etc.¹⁹² In the wake of the 2020 lockdown, unique telemedicine -based care models of care have been developed to meet the care needs of elderly Africans. In Nigeria for instance, a “Care in Place” policy was implemented in a pioneering geriatric centre. This involved the provision of home based care for ambulatory geriatric patients in order to prevent avoidable hospital visits and with

the attendant risk of infection with the virus.¹⁹⁵ Other recommendations from the Lancet Commission¹⁹⁴ on dementia prevention, treatment and care and dementia experts¹⁹⁰ are generally applicable within the African context.

5. THE AFRICAN DEMENTIA CONSORTIUM

The broad aim of the African Dementia Consortium (AfDC) is to bring together African dementia researchers in a multidisciplinary framework and generate clinical, cognitive, socioeconomic, neuroimaging, genomic and biomarker data to improve the phenotypic characterization of dementia in Africans. The network will also identify novel biomarkers and interventions for prevention and treatment. The AfDC will further foster the translation of evidence to policy and practice and contribute to efforts to reduce the burden of dementia among Africans, African ancestry populations in Diaspora and ultimately contribute to the reduction of the global burden of dementia.

In order of priority, AfDC will focus on research areas including: (1) epidemiological studies to define trends in prevalence, incidence, and risk factors for dementia in Africa; (2) genetic studies to unmask novel variants that predispose to Alzheimer's disease and related dementias (ADRD) in African populations and also increase African participation in global genomic studies including trans - ancestry meta analyses in dementia; (3) detection of unique biomarkers for dementia; (4) conduct of dementia clinical trials involving African populations; (5) capacity building and networking among dementia researchers living or working in Africa particularly early career investigators; (6) facilitation of translational dementia research (7) promotion of implementation science for translation of research evidence to practice and policy in Africa and (8) training and education of the next generation of research leaders. The consortium will build effective synergies through collaborative research networks with researchers within Africa and with partners from North America, Latin America, Europe, Asia and other regions of the world.

6. CONCLUSIONS

It is imperative that we invest resources to better reduce the current vast gaps in knowledge regarding Alzheimer's and other dementias in the African continent. The ageing of the population makes this an economic and social, as well as a moral and ethical imperative. Furthermore, undertaking further genetic, biomarker and pathological studies in this genetically and environmentally diverse region promises to lead to an improved understanding of the biology of AD that will benefit individuals and populations all over the world and further promote effective prevention, treatment and care as recently outlined by the Lancet Commission on Dementia.¹⁹⁴ Equity in access to dementia diagnosis, treatment and access to care as well as dementia prevention strategies should remain core to the future efforts engaged in dementia science and care in Africa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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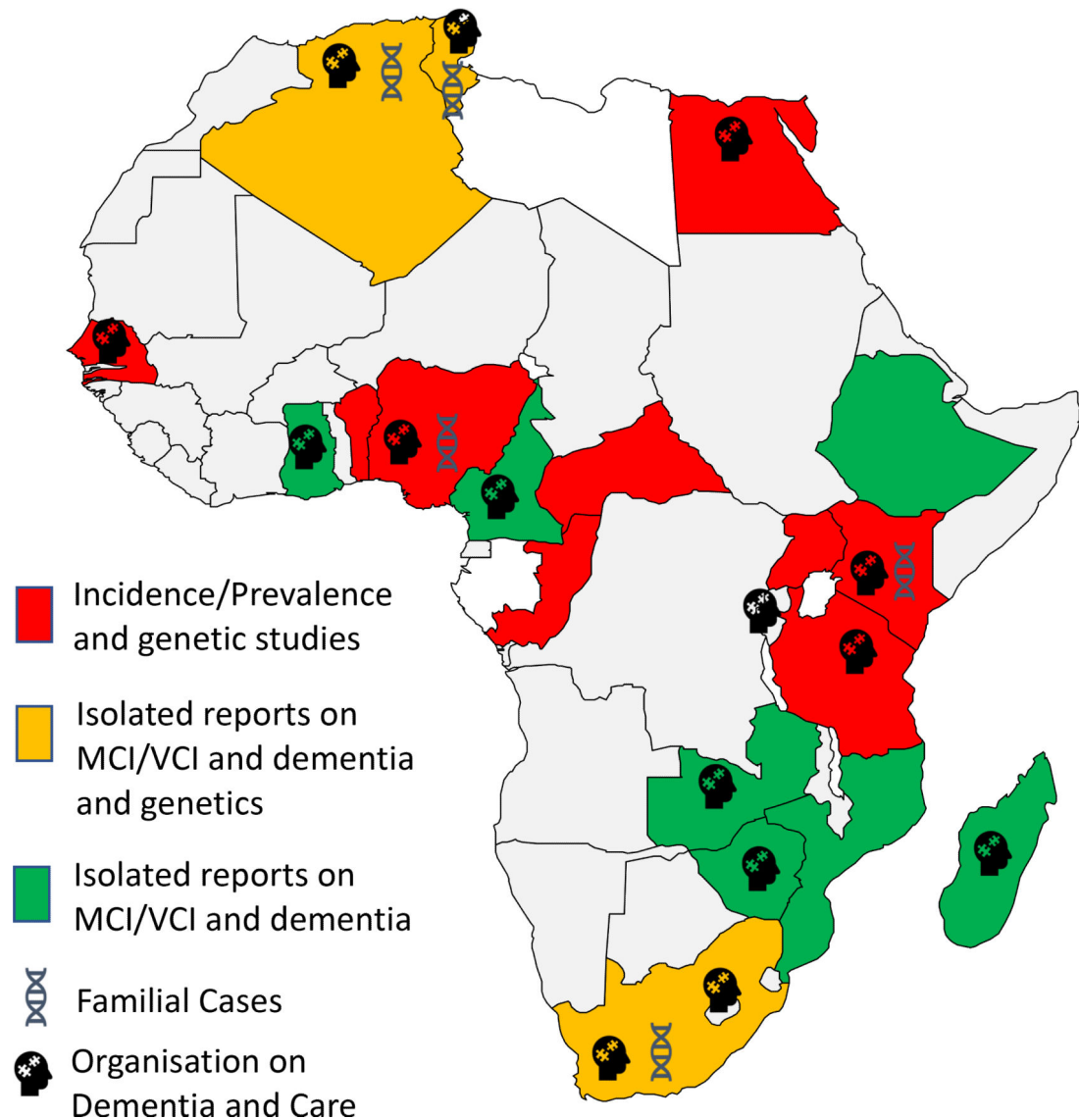


Figure 1: Dementia in Africa and Dementia Care and Support Organisations

Map of Africa showing limited number of countries where incidence and prevalence studies have been conducted over the past 30 years. Some countries have reported isolated reports on dementia cases in particular Alzheimer's disease or vascular dementia. Limited number of countries in which candidate gene investigations have been carried out. In several African countries dementia care and support organisations exist. Most of these are member organisations of ADI (<https://www.alzint.org>). Further reports of cases and deaths due to dementia in African countries are known (www.afro.who.int) but are not published in peer-reviewed sources.

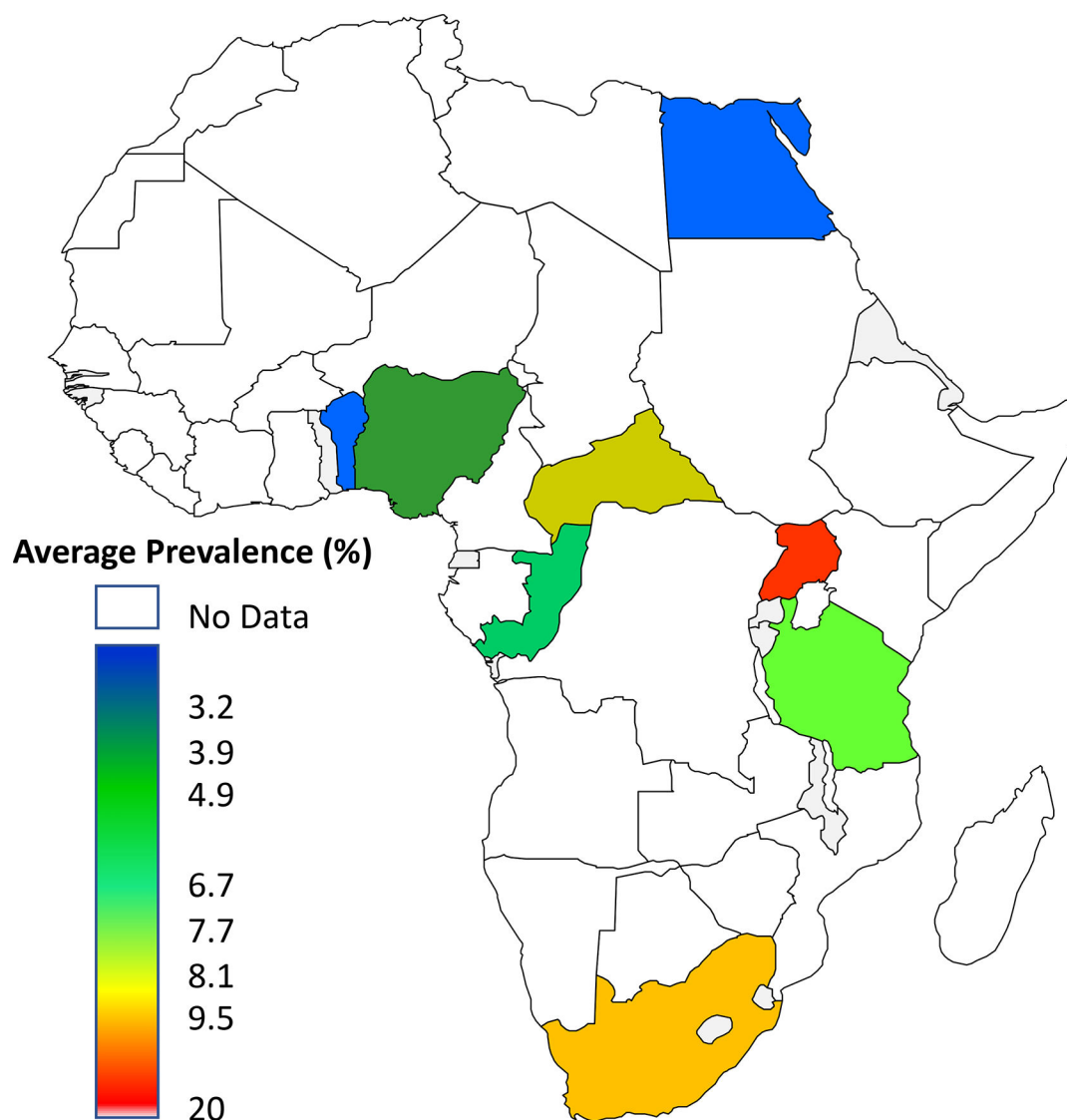


Figure 2: Prevalence of Dementia in Africa

Heat map showing wide range of dementia prevalence in African countries determined over the past 25 years. Dementia prevalence studies have also been conducted in Senegal and Kenya but the data are not published yet.

Table 1:

Summary of community-based epidemiological studies of dementia in Africa

Author/Site, Country	Year	Criteria	Sample (n)	Age (yrs)	Prevalence			Identified Risk Factors	Limitations
					Dementia	AD	VaD		
West Africa									
Hendrie et al ²² /Ibadan, Nigeria	1995	DSM III-R ICD 10	2494	65	2.3%			-	No consideration for educational status. Cultural bias in diagnosis. High rate in Indianapolis cohort. Age was determined using historical landmarks.
Ogunniyi et al ¹⁶ /Ibadan, Nigeria	1997	DSM III-R ICD 10	2494	65		64.3%	28.6%	-	Age was determined using historical landmarks. High illiteracy rates. No radiological confirmation
Hall et al ⁶³ /Ibadan, Nigeria	2006	DSM III-R ICD 10	1075	70				Dyslipidemia.	Small number of AD cases. Survivor bias as most of the attrition from earlier cohort were due to mortality. Criteria for control group uncertain. Cross-sectional design not appropriate to determine association
Ochayi and Thatcher ⁷⁸ /Jos, Nigeria	2006	CSID	280	65	6.4%			Age, Female sex, BMI, NSAIDs	Possible over-estimation of dementia rate due to one stage process used. Wide confidence intervals for estimates. Estimated ages. Cross-sectional design.
Gureje et al ²⁰ /Southwest, Nigeria	2006	10-WDRT DSM IV	2152	65	10.1 %			Age, Female sex, Lifetime history of alcohol use	Cross-sectional design. Incomplete information about disabilities.
Guerchet et al ²⁴ /Djidja, Benin	2009	DSM-IV	514	65	2.6%	53.8%	7.7%	Age	Self-reported education. Informal age confirmation. Cross-sectional design. Low proportion of subject schooled. No radiological confirmation
Yusuf et al ²⁶ /Zaria, Nigeria	2011	DSM IV ICD 10	322	65	2.8%	66.7%	33.3%	Age	One stage selection. No radiological confirmation
Paraíso et al ²⁵ /Cotonou, Benin	2011	DSM-IV	1162	65	3.7%			Age, Female sex	Sub-section of CSI-D used. Neuropsychology test do not have adjusted normative values for illiterate population. Relatives not involved to confirm details
Gureje et al ³⁷ /Southwest, Nigeria	2011	10-WDRT CHIF	1225	65				Age, Gender, Poor economic status, Rural Living, Social Isolation	Preponderance of persons with little or no education. Use of 10-WDRT
Akinyemi et al ⁴¹ /Ibadan and Abeokuta, Nigeria	2014	DSM-IV ASA/AHA	143 (Stroke survivors)	.45			8.4%	Age, Low Education, Medial temporal lobe atrophy, Pre-stroke cognition	Modest sample size. Incomplete neuroimaging.
Ogunniyi et al ⁴² /Lalupon, Nigeria	2016	DSM-IV	613	65	2.9%	58.8%	11.7%	Age	Lack of neuroimaging. Identification of treatable conditions

Author/Site, Country	Year	Criteria	Sample (n)	Age (yrs)	Prevalence			Identified Risk Factors	Limitations
					Dementia	AD	VaD		
Ojagbemi et al ¹⁵ /Southwest, Nigeria	2016	10-WDRT CHIF	2149	65				Age, Gender, Socioeconomic status, Pre-existing cognitive decline, Occupational complexity.	Inaccurate survival data. Attrition. Small size of dementia mortality sample
Sarfo et al ⁴⁰ /Kumasi, Ghana	2017	DSM-IV	147 (Stroke survivors)					Age, Education, Functional ability	Modest sample size. Cross-sectional study. Neuroimaging not available for review. Lack of pre-stroke cognitive status.
Adoukonou et al / Parakou, Benin	2020	DSM-IV-TR	440	50	3.2%	64.3%	21.4%	Age, Living alone, Low vegetable intake	Not generalizable. Verbal report of vascular factors. Participants may have benefitted from having a better socioeconomic status and better access to health care than the overall older population. Sample size was small. High level of refusals. Use of the brief version of the CSI-D also carries some limitations.
Central Africa									
Guerchet et al ²⁷ / Bangui, CAR	2010	DSM-IV	496	65	8.1%	82.5%	17.5%		DSM-IV underestimate. No radiological confirmation
Guerchet et al ²⁷ / Brazzaville, Congo	2010	DSM-IV	520	65	6.7%	68.6%	31.4%		
Guerchet et al ⁶⁵ / Bangui CAR and Brazzaville, Congo	2012	DSM-IV	977	65	7.6 %			Age, Female sex, Hypertension, Peripheral artery disease, Low BMI, Depression, Lack of education	High rate of missing data. Cross-sectional design. Absence of <i>APOE</i> genotyping. No radiological confirmation
East Africa									
Longdon et al ²⁹ /Kilimanjaro, Tanzania	2013 2014	DSM-IV	1198	70	6.4%	48.7%	41.0%	Diabetes	No radiological confirmation. Incomplete radiological and laboratory investigations. Too little number for subtypes. Attrition. Non-medically trained census enumerators.
Mubangizi et al ³⁰ /Rural Southwest, Uganda	2020	Brief CSID	400	60	20.0%			Age. But having some education, exercise and ventilated kitchen were protective	No structured clinical interviews. Brief CSID used. Early and midlife exposure variables were measured by self-reporting.
Yoseph et al ¹⁶² /Kilimanjaro, Tanzania	2021	DSM- V	3011	70	8.9%			-	
South Africa									
Ramlall et al/Nursing Homes, South Africa	2013	DSM-IV-TR	140	60	7.9%		40.0%	Blackouts, Hypertension, Exercise, Visual and Hearing impairment.	Poor sampling – small size, low number of black participants, low number of dementia cases. Inter-rater reliability not quantified.

Author/Site, Country	Year	Criteria	Sample (n)	Age (yrs)	Prevalence			Identified Risk Factors	Limitations
					Dementia	AD	VaD		
De Jager et al ¹³ / Amatole District, South Africa	2017	CSID	1394	65	11.0%			Older age, depressive symptoms	No clinician resources to provide a DSM-IV diagnosis of dementia. Targeted sample size not achieved. Sampling involved only low-income rural community
North Africa									
Farrag et al ³⁴ / Assiut Governorate, Egypt	1998	DSM-III R	2000	60	4.5%	53.0%	22.9%	-	NS
El Tallawy et al ²³ / Al Kharga District, Egypt	2012	DSM-IV-TR	8173	50	2.3%	51.2%	28.7%	-	NS
El Tallawy et al ³² / Al-Quseir city, Egypt	2014	DSM-IV	4329	50	3.8%	48.3%	36.8%	-	NS
Khedr et al ³³ / Qena Governorate, Egypt	2015	DSM-IV	619	60	5.1%	34.3%	25.7%	-	NS

Abbreviations: DSM- IIIR – Diagnostic & Statistical Manual of Mental Disorders–3rd Edition Revised; ICD- 10 – International Classification of Diseases 10th Revision; WDRT - 10-Word Delayed Recall Test; CHIF - Clinician Home-based Interview; DSM – IV - Diagnostic & Statistical Manual of Mental Disorders– 4th Edition; DSM – IV-TR- Diagnostic & Statistical Manual of Mental Disorders– 4th Edition Text Revision; CSID – Community Screening Instrument for Dementia; CAR – Central Africa Republic; NS - not stated

Table 2:

Candidate gene studies for dementia phenotypes in Africa

Authors (year)	Gene Name	Study Population	Salient Findings
Osuntokun et al (1995) ⁴⁴	<i>APOE ε4</i>	Yoruba Nigerian	No association was reported between <i>APOE ε4</i> alleles and AD
Lane et al (2003) ⁵²	<i>APOE ε4</i>	African American and Yoruba Nigerian	No association was observed between <i>APOE ε4</i> alleles, age and mortality risk among the Yoruba Nigerians.
Heckmann et al (2004) ⁵⁶	<i>PSEN1</i>	Southern Africa	<i>PSEN1</i> mutations associated with early onset AD but no effect of <i>APOE ε4</i>
Momeni et al (2006) ⁵⁷	<i>CHMP2B</i>	South African	Mutation in <i>CHMP2B</i> gene associated with frontotemporal dementia
Gureje et al (2006) ⁴⁵	<i>APOE ε4</i>	Nigerian	Lack of association between <i>APOE ε4</i> and AD
Chen et al (2008) ⁴⁶	<i>APOE ε4</i>	Kenyan	Lack of association between <i>APOE ε4</i> and AD
Guerchet et al (2009) ²³	<i>APOE ε4</i>	Beninoise	No association between <i>APOE ε4</i> and cognitive decline
Hoare et al (2013) ⁵³	<i>APOE ε4</i>	South African	<i>APOE ε4</i> is associated with memory impairment and white matter integrity in HIV positive individuals
El Kadmiri et al (2014) ⁵⁴	<i>APP</i>	Moroccan	7 novel mutations (frameshift mutations) in the <i>APP</i> gene on exons 16 and 17 had genetic contributions to AD
El Kadmiri et al (2014) ⁵⁵	<i>PSEN1, PSEN2</i>	Moroccan	Mutations in both genes have a genetic effect on early onset AD
Hendrie et al (2014) ⁴⁸	<i>APOE ε4</i>	African Americans and Yoruba Nigerians	One or two copies of <i>APOE ε4</i> allele is/are significant risk for both AD and cognitive decline in African Americans. Only homozygous carriers of the <i>APOE ε4</i> among Yoruba Nigerians had a significant risk factor for AD but not cognitive decline
Fekih-Mrissa et al (2017) ⁵⁹	<i>PAI 1</i>	Tunisian	Variants of <i>PAI-1</i> had significantly increased risk for AD. Homozygotes are at higher risk while female gender was also at increased risk.
Landoulsi et al (2018) ⁵⁸	<i>TREM2</i>	Tunisian	<i>TREM2</i> has no association with late onset AD which has significant risk in Caucasian populations
Haihem et al (2018) ⁴⁷	<i>APOE, ACE1, PONI</i>	Tunisian	All studied genes had polymorphisms associated with dementia risk individually and collectively with a cumulative and synergistic effect

Abbreviations: *APOE* – Apolipoprotein E; *PSEN1* – Presenilin 1; *PSEN2* – Presenilin 2; *APP* – Amyloid Precursor Protein; *CHMP2B* – charged multivesicular body protein 2B; *PAI 1* – Plasminogen activator inhibitor-1; *TREM2* – Triggering receptor expressed on myeloid cells 2; *ACE1* – Angiotensin-converting enzyme; *PONI* – Serum paraoxonase and arylesterase 1.