The 23rd Benjamin Oluwakayode Osuntokun Memorial Lecture

Solving the Dementia Puzzle: Ibadan's Contributions and the Challenges of Contemporary Relevance

Adesola Ogunniyi
Professor of Medicine (Neurology)
Department of Medicine
College of Medicine
University of Ibadan
Ibadan

6th January 2022

This monograph is published as part of the annual lecture series of the Benjamin Oluwakayode Osuntokun Trust.

The Benjamin Oluwakayode Osuntokun Trust
University of Ibadan
U.I. P.O. Box 9388
Ibadan, Nigeria

The 23rd Benjamin Oluwakayode Osuntokun Lecture
6 January 2022

Solving the Dementia Puzzle: Ibadan's Contributions and the Challenges of Contemporary Relevance

by

Adesola Ogunniyi
Professor of Medicine (Neurology)
Department of Medicine
College of Medicine
University of Ibadan
Ibadan

ISBN: 978-978-921-227-9

The Benjamin Oluwakayode Osuntokun Trust, Ibadan
c/o Professor O. Osuntokun
U.I. Post Office Box 9388
University of Ibadan
Ibadan, Nigeria

Published in Nigeria by
BookBuilders • Editions Africa
2 Awosika Avenue, Bodija, Ibadan
email; folatundeus@yahoo.com
mobile: 08068052154

Printed in Ibadan
Oluben Printers, Oke-Ado
mobile: 0805 522 0209

Introduction

I am extremely grateful for the honour of being selected to give the 23rd Benjamin Oluwakayode Osuntokun Memorial Lecture to celebrate the life of an icon in neuroscience and my mentor. Today would have been his 87th birthday, but he passed on at an early age of 60 years, when we needed him most, but God loved him more and we cannot query that. We continue to miss the great contributions and his impact on the lives of many of us during his lifetime. May his great soul continue to rest in perfect peace.

I had a meeting with Professor Olabopo Osuntokun, Chairperson of the BOO Trust, on 3 June 2021, and had thought it was to deliberate on who the 2022 lecturer would be, as well as to plan other details of the arrangements, which was the usual practice. Little did I know that the decision had been made that I would be the one taking the centre stage. Prof Benjamin Oluwakayode Osuntokun's (BOO) legendary achievements in Medicine and Neuroscience had been extolled in previous lectures and I would not repeat many of the attributes. Suffice it to say at this stage that his academic contributions were acclaimed nationally and internationally. He was the recipient of the National Order of Merit in 1984 and Nigeria's Centenary Award for Academic Excellence in 2014. He was the Chairman, Global Advisory Committee on Health Research of the World Health Organization, which was no mean achievement. Even after twenty-five years of his death, he continued to be regarded as the most influential

neuroscientist from Nigeria. One of his lasting legacies was the description of congenital pain asymbolia with auditory imperception, which eponymously bears his name. He combined his academic talents with being a great administrator as Dean of Ibadan Medical School (1974 - 78), Medical Director of Aro Neuropsychiatric Hospital, Abeokuta (1983 - 85) and Chief Medical Director, UCH, Ibadan (1985 - 90). His tenure in these different positions witnessed tremendous changes.

I was fortunate to work closely with him for about 17 years and I am leveraging on this to present first-hand information as someone who drank from his fountain of knowledge. At various stages in my career, he was my teacher, supervisor, role model, adviser and cheerleader. I completed my undergraduate medical education at the then University of Ife (now Obafemi Awolowo University), and I was one of the four fresh graduates of the Ife programme that was selected for internship at the University College Hospital, Ibadan. Through providence, I was posted to the Neurology Unit, which was quite daunting. I had followed the exploits of Prof Osuntokun (BOO) and his publications on cassava neurotoxicity that led to the award of the Doctor of Science of the University of London in 1977, which made the headlines. I was therefore awed to be posted to his unit, and that set the stage for great academic and mentoring experience under this internationally-acclaimed giant.

BOO excelled in the way and manner he conducted ward rounds, clinic sessions and teachings. He dazzled us with his knowledge of both basic and clinical neuroscience, and was

always willing to teach us so that we could be like him. His write-ups on patients were so detailed that one marvelled at his mastery of Medicine, how long it took him to obtain all the vital information in every case, and the painstaking documentation of his clinical findings which surpassed what we younger ones could do. I vividly recalled one occasion when he documented that a patient had cranial nerve deficits among other signs, and the admitting Registrar not only failed to identify the cranial nerve deficit but had the temerity to write in the case note that: "no abnormality was detected" abbreviated as "NAD" on cranial nerve examination of that patient. BOO read through the case file, and gently changed the NAD to "not actually done". Indeed, he did not suffer fools gladly. We all then knew that we had to be meticulous in our assessment and documentation on patients as well as their management. We revered him for his intellect and work ethic, because it appeared that he worked round the clock and he was very current with the latest information in medical literature, which he shared with us during various academic sessions. He believed in active learning; because to him, "to hear is to forget, to see is to remember, and to read is to know". We were thus inspired to read and be abreast of developments in Medicine. Professor Olajide Bademosi always ensured that we were cognitively fortified and adequately prepared for interactions with BOO, which certainly helped a great deal.

Despite his busy schedule, BOO found time to coach Ranti Familoni, Yomi Akanji, Olatunde Odusan, Kehinde Akinlade and I for the Part I fellowship examinations in 1982,

and we passed. I was his Senior Registrar in Neurology, and he gladly supervised my Part II dissertation titled "Risk Factors for Epilepsy in Nigeria'. I utilized the WHO protocol that he developed with Bruce Schoenberg and Liana Bolis for data collection. When the year-abroad programme of the National Postgraduate Medical College of Nigeria was phased out around 1984, my plan to go to the Montreal Neurology Institute, Canada was dashed because of shortage of funds, even at that time! He immediately organized a Neuroepidemiology Fellowship for me at the National Institutes of Health, Bethesda under Bruce Schoenberg, which changed the trajectory of my career for good. I changed from being just a clinical neurologist to a clinician, researcher and neuroepidemiologist, all combined, for which I am forever grateful. Indeed, he was a man with the Midas touch in networking, grant sourcing and collaboration, who undertook nothing without adorning it.

He was the giant on whose shoulders I stood to see the world of neuroscience and the academic Medicine with conference attendance/presentations and publications. When I won the Bruce Schoenberg International Neuroepidemiology Award of the American Academy of Neurology in 1991 for our first community-based study on the prevalence of dementia in Idikan, he was there in Boston, at his own expense, to support me as I was green to presentations at that level. He reviewed my slides and approved them before the presentation. He introduced me to Professor John N. Walton, Lord Walton of Detchant, his former teacher at Newcastle and past President of the

General Medical Council of Britain. Lord Walton remarked that he had not heard my name before to which BOO gently replied that being associated with him was sufficient recognition. I can go on and on listing all the things he did to boost my ego and enhance my career. I vividly recall various sponsored travels for conference attendance/ presentation in Accra (1988), Florence, Zaragoza, Liverpool, New Delhi (1989), London (1990), Boston (1991), Vancouver (1993) and Minneapolis (1994), which opened my eyes and broadened my horizon. Each trip was a learning experience on devotion to work, research collaboration, data analysis, presentation styles and anecdotes that were suitable for different occasions.

He was truly a role model and always inspiring. It was not "all work, and no play", as he invited some of us on many occasions to his house to discuss our plans, to celebrate landmark achievements and to generally unwind, especially during inter-site visits of research collaborators. His well-stocked library was always a choice-place to stay in, quite understandably, to read the latest in medical literature. I found such sessions very relaxing and as opportunities to know him better. Those were really interesting times indeed, and I missed them.

Therefore, being asked to deliver this lecture gives me immense pleasure as his mentee. My aim is to present what we accomplished in dementia research, which was his brain-child. The first part of the lecture will provide some basic understanding of dementia, while the second part will highlight the contributions of Ibadan researchers (during and

after BOO). The concluding part will show challenges of matching current and global practices in dementia diagnosis, prevention and treatment.

Cognitive Disorders

Cognition, defined as the mental action or process of acquiring knowledge and understanding through thinking and the use of the senses[1], has been aptly described as the last frontier in neuroscience. Individuals who suffer from cognitive disorders continue to challenge us because of the varied and perplexing presentations, complex pathogenesis and the heartache of finding a cure. The domains of cognition are memory, learning, orientation, communication, executive function (comprising abstraction, judgment and calculation), visuo-spatial ability, complex attention and social cognition. Cognitive disorders are classified along a spectrum, from subjective cognitive impairment through mild cognitive impairment to dementia, at the other extreme.

Dementia is a clinical syndrome comprising cognitive deficit (memory, language, judgment, etc) and impairment in social or occupational functioning, in the conscious and alert state[2]. Dementia, which can be described in simple terms as "loss of mind", "brain failure", "brain fog" or "being senile", is a disease and not part of normal ageing as some individuals think. The word "dementia" has gained a lot of prominence in recent times and has slowly crept into everyday usage. The American Psychiatric Association in the latest Diagnostic and Statistical Manual (DSM-V) used the terminology "major neurocognitive disorder" for dementia

so as to reduce the negative stereotype associated with the condition[3].

Understanding Dementia

Dementia affects between 5% and 11% of individuals aged 65 years and over in western countries. Recent prevalence estimates using a lower cut-off age of 60 years has brought down the rate to 4.7% and regional estimates as 2.6% in Africa, 4.0% in Asia, 6.2% in Europe and 6.9% for North America[4]. Dementia is classified into degenerative, vascular and reversible types. Degenerative dementia results from the death of neurons, loss of synapses, neurotransmitter deficiency and abnormal protein deposition in the extra- and intra-neuronal spaces. The hallmark is generalized or circumscribed brain atrophy due to death of neurons. The pathogenetic mechanisms underlying neurodegeneration are programmed cell death (apoptosis), vascular insufficiency, oxidative stress, inflammation and excitotoxicity. Examples of neurodegenerative dementia are Alzheimer's disease (AD), fronto-temporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), Huntington's disease (HD), Parkinson's disease with dementia (PDD) and Creutzfeldt-Jakob disease (CJD). The clinical types are differentiated by the predominant presenting features, the pattern of progression and neuroimaging findings, as shown in Table 1. Some cases of degenerative dementias have been reported in Nigeria,[5,6,7,8] but prion's diseases are relatively uncommon in sub-Saharan Africa (SSA).

Table 1. Clinical types of dementia

Type*	**Predominant clinical features**	**Pattern of progression**	**Pathology**
AD	Memory loss predominantly	Progressive	Amyloid deposition, elevated CSF tau protein; brain atrophy
VD/VCI	Focal deficit, executive dysfunction	Step-ladder	Infarcts, lacunes, white matter changes, microbleeds, subcortical and cortical
FTD	Behavioural and language problems	Progressive	Circumscribed atrophy of the brain, astrogliosis, inclusions (Pick's bodies); progranulin, TDP-43
LBD	Visual hallucinations, non-motor Parkinsonian features	Fluctuation	Lewy bodies, alpha-synuclein deposition, brain atrophy
PDD	Slowness, rigidity, memory loss and executive dysfunction	Progressive	Depigmentation of substantia nigra, Lewy bodies
HDD	Chorea + cognitive dysfunction	Progressive	Atrophy of caudate nucleus, astrocytosis; trinucleotide repeats

*AD = Alzheimer's disease; VD = Vascular dementia; VCI = Vascular Cognitive Impairment; FTD = Fronto-temporal dementia; LBD = Lewy Body dementia, PDD = Parkinson's disease dementia, HDD = Huntington's disease dementia

Alzheimer's disease is of particular interest because it is the most common type of dementia (figure 1), and it predominantly affects memory. The distinguishing pathological feature is the deposition of amyloid plaques and tangles (abnormal phosphorylated tau protein) within the brain, with associated brain atrophy. Possession of certain

genetic traits such as amyloid precursor protein gene (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) increases the potential for developing AD. Apolipoprotein E on chromosome 19 is associated with cholesterol transport in the brain and with amyloid deposition. Other genetic traits include chromosome 17 for FTLD and chromosome 4 for HD.

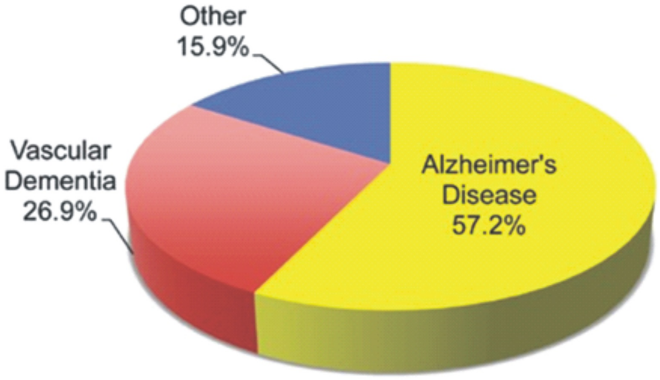

Figure 1. Dementia types in Africa (Ref. 48).

Dementia may also be consequent upon cerebrovascular disease (Vascular Dementia or Vascular Cognitive Impairment), which may follow single or multiple strokes. Lastly, there are many treatable or reversible types which are secondary to brain diseases like tumours, subdural collection, normal pressure hydrocephalus, biochemical derangements following terminal organ diseases or abnormal glucose metabolism and electrolyte imbalance. Infections, especially the human immunodeficiency virus infection (HIV) and medication side effects in the elderly are also important

treatable causes in low-resource settings. The exclusion of treatable lesions is essential before thinking of the untreatable neurodegenerative diseases.

Clinical Features of Dementia

The common manifestations are forgetfulness (names, dates, appointments), muddled thinking, difficulty naming objects, problems with calculation and interpretation of proverbs, struggling to keep track of time, needless repetition of stories, difficulty finding the way in an otherwise familiar neighbourhood or even getting lost. Functional impairment manifests as problems with handling finances, medications, cooking, difficulty with participating in social and religious activities, inability to give advice and, in later stages, problems with feeding, dressing and with personal hygiene. Dementia can be quite perplexing as illustrated by George Elliot in his description of Romola[9]:

> Would anyone believe that he had ever had a mind filled with rare knowledge, busy with close thoughts, ready with various speeches? It had all slipped away from him – that laboriously gathered store. But he found to his acute distress, that of the new details he learned he could only remember a few, and those only by continual repetition; and he began to be afraid of listening to any new discourse, lest it should obliterate what he was already striving to remember…

In the advanced stage, constant care must be provided as the affected person is bereft of all senses and is prone to

infections, home accidents and elder abuse. The sufferer is described as being dehumanized because of loss of all human dignity.

That in essence is what happens when an individual develops Alzheimer's disease (AD). The memory loss can lead to inopportune mistakes and may be accompanied by certain behavioural changes that baffle family members. It is obvious that our ability to remember events and loved ones gives human life dignity, meaning and, above all, it is essential for wisdom. Without good memory, the joy of living is lost and the human pride is lost. This is best captured in this lifeline SNAPSONG of Nigeria's literature icon, Professor Niyi Osundare[10]:

> What's there to choose between those who remember too much and those who remember not at all?
> Can memory be a millstone around our neck or that much desired stepping stone to the house of wisdom?
> What happens to the Beauty Queen who forgets her face at home, or the lion with a missing mane in the gathering of champion cats?
> How do we console the Orator who falls from the tree of words, how do we sew the rags of his broken syntax?
> When memory sleeps, it is remembrance that keeps it awake like the stick which provokes the drum.…

Why the Global Attention on Dementia?

Dementia, regarded as a public health priority by the World Health Organization[11], is attracting a lot of interest worldwide for the following reasons:

- **The rapid increase in the number of cases globally.** It is estimated that a new case is added every 4 seconds and about 8 million cases annually, according to the Alzheimer Disease International (ADI). Therefore, the number of persons living with dementia will nearly double every 20 years. The total number of cases is projected to increase from approximately 47 million people in 2015 to 131 million by 2050. In sub-Saharan Africa (SSA), an increase of over 250% is expected in the absolute number of cases during that same time period from 2.13 million to 7.62 million[12]. Adeloye and colleagues calculated a 400% increase in dementia cases, rising from 63,512 to 318,011 among persons aged ≥60 years in Nigeria between 1995 and 2015 from computer modeling[13]. The disproportionate burden of dementia cases in low- and middle-income countries (LMIC) with the constraints of limited trained manpower and meagre resource allocation to health is of utmost concern.
- **Demographic transition with an increase in the number of aged individuals at risk of developing dementia**. The United Nations projected that between 2015 and 2050, the number of individuals aged 60 years and above in Africa will increase from 46 million to 220 million[14].
- The terminal stage of dementia leaves affected individuals bereft of all senses and in need of constant care.
- The lack of cure currently for a disease that steals the mind.

- **The enormous cost of providing care, which is largely borne by family members in most LMICs because of limited resources for the care of the elderly.** The total cost of care (direct medical, social and informal care) for cases in SSA was put at US$ 6.2 billion in 2015 by Wimo et al. The worldwide cost of dementia was reported to have risen by 35% between 2010 and 2015, due to large increase in the number of cases and was projected to have surpassed one trillion US Dollars in 2018[15]. Over 80% of the cost is spent in high-income countries.
- **The stigma associated with the disorder**. In a qualitative study carried out by Adebiyi and others in Lalupon, Oyo State, many participants referred to dementia as a disease of insanity and dull brain. Thirty-six percent of the participants felt that dementia was associated with shame and embarrassment in the community and another 28% opined that those individuals with dementia should not be taken seriously[16]. Another study by Nwakasi and colleagues reported misconceptions about dementia and that the associated stigma adversely affected care provision[17].

Ibadan's Contributions to Dementia Research

The main aim of this lecture is to highlight the pioneering work of BOO in dementia. Contributions from three funded studies: Indianapolis-Ibadan Study: 1991-2011 (PI: Hugh Hendrie and BO Osuntokun at inception, later Prof ABOO Oyediran, Kathleen Hall and A. Ogunniyi/Segun Baiyewu), Ibadan Study of Ageing: 2009- 2016 (PI Oye Gureje) and the

Identification and Intervention for Dementia in Elderly Africans (IDEA Study): 2013-2019 (PI: A. Ogunniyi) will be showcased. Lastly, the recent meta-analysis by Akin Ojagbemi and his colleagues putting an African perspective to dementia research will be mentioned. The intention is to synthesize the findings from these studies to present, in some detail, the contribution of Ibadan researchers to unravelling the unknown about dementia.

Preliminary Studies (1984-1991)

Diseases do not respect geographic boundaries, particularly dementia, which does not respect country, gender, political or socioeconomic status. Anyone with the underlying predisposition and the neuropathologic features described above could develop dementia. The interest in dementia began with the impressionistic view that AD was rare in Nigerians, which was cited by Henderson in his review published in the British Medical Bulletin in 1986[18]. He echoed BOO's thought that there seemed to be grounds for the hypothesis that senile dementia of Alzheimer's type was a Western disease and the consequence of some exposure to which the species was not adapted because the illness appeared to be uncommon. It was inconceivable that a particular ethnic group would be biologically advantaged and immune from developing such a terrible disease that was a challenge to the world. That led to a flurry of research activities that involved comparative histological study of amyloid in the brains of elderly Nigerians and Australians, as well as cross-cultural studies initiated by the World Health

Organization. In the interim, between 1986 and 1987, we developed and validated the Yoruba version of the Mini-Mental State Examination (MMSE), with carefully-selected, culturally-appropriate test items[19]. This was a necessary step for documenting cognitive impairment because most of the tools available then were educationally- and culturally-biased. The Yoruba version of the MMSE that we developed was used for the initial community survey of dementia in Idikan in 1989.

The Nigerian-Australian study took place between 1989 and 1990, and resulted from a collaboration between Colin Masters of Melbourne University and BOO. It involved comparative morphological analysis of immunofluorescent-stained paraffin sections of brains for amyloid deposits. The brain specimens were obtained from 111 Nigerians and 99 Australians with normal cognition ante mortem, aged 50 years and above. The finding was that amyloid existed in the brains of elderly Nigerians, but was less frequent and less severe than in the brains of age-matched Australians (figure 2)[20]. Raj Kalaria and colleagues in East Africa also demonstrated the presence of amyloid in the brains of elderly Kenyans, but quantitation was not done[21]. Therefore, there must be other reasons why AD appeared to be relatively uncommon in Africans. One quick explanation was the relatively young population.

The next phase was the planning of collaborative cross-national studies by the WHO. Experts were invited from Canada, Malta, Nigeria, USA (Indianapolis), Spain and Chile for cross-cultural comparisons that could lead to solving the

environmental puzzle in terms of risk factors and cultural practices. I accompanied BOO on the trip to the meeting in Zaragoza, Spain in 1989, where the idea of Indianapolis-Ibadan collaboration was conceived.

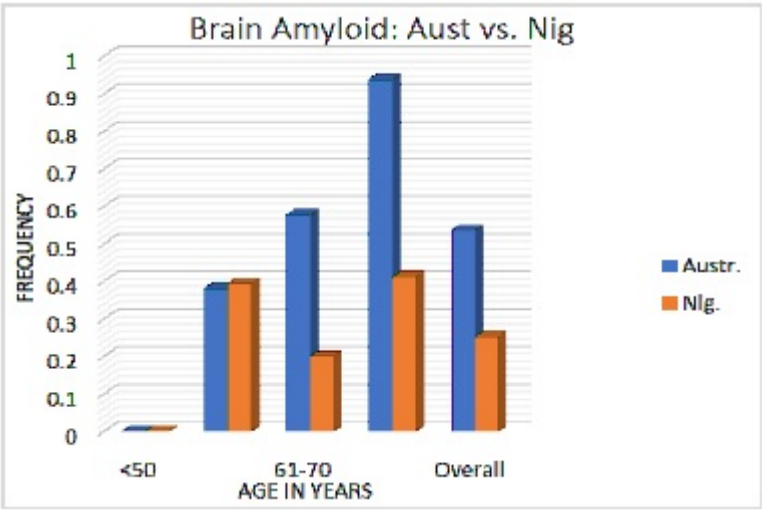

Figure 2. Brain amyloid among Australians and Nigerians.

Indianapolis-Ibadan Study (1991-1995)

BOO's hypotheses were:

- that comparative cross-cultural, transnational, geographic epidemiologic studies would be useful in delineating the true risk factors for age-associated dementias, particularly AD, and
- that the identification of populations or communities with significantly lower or higher prevalence rates of AD could greatly enhance the search for environmental risk factors[22].

These formed the basis of the Indianapolis-Ibadan collaboration in which community-dwelling African Americans and Yoruba, aged 65 years and above, were studied prospectively. The multidisciplinary study involved neurologists, psychiatrists, clinical psychologists, epidemiologists, nutritionists, social workers, nurses and biostatisticians. Culturally-appropriate instruments were developed and operationalized:

- Community Screening Interview for Dementia (CSID)[23], a robust test for various cognitive domains in populations with low literacy levels was developed and validated. It contained test items from the Yoruba MMSE and the Cambridge Mental Disorders of the Elderly Examination (CAMDEX),
- Stick Design for testing visuo-constructional ability[24],
- IU Token Test for assessing executive functioning, and
- Clinician Home-based Interview to assess Function (CHIF) for assessing functional impairment bearing in mind technological limitations and cultural relevance.

The study design involved a two-phase evaluation (initial screening followed by clinical assessment) at each wave followed by consensus diagnosis by researchers from both sites. Dementia diagnosis was based initially on DSM-III- R criteria, and subtyping according to the NINCDS-ADRDA criteria for AD, and ICD-10 criteria for the other types[25].

Burden of Dementia

The prevalence study took place simultaneously in Indianapolis and Ibadan, with 2212 and 2494 consenting participants, aged 65 years or over enrolled respectively. The prevalence rates of dementia and AD were 2.29% and 1.41% respectively in the Yoruba compared with 8.24% and 3.25% in the African Americans[25]. The prevalence estimates in the Yoruba were among the lowest reported in the world at that time and was in keeping with the earlier impression of lower dementia burden. This was the first community-based, dementia prevalence study in SSA and it paved the way for further studies in other communities/regions in Nigeria as well as other countries in SSA. The significant differences in rates between cohorts that had genetic similarities but living in different environments brought to the fore a need to search for environmental influences, as BOO had postulated. The model proposed by Cooper and Kaufman in their study of hypertension in blacks of gene-environmental interactions[26] was then employed to tease out the possible genetic and environmental factors at play.

One genetic factor that received great attention in 1993 was apolipoprotein E (APOE), which was first reported to be associated with late-onset sporadic AD by researchers led by Alen D Roses at Duke University, USA. APOE exists as 3 alleles (2, 3 and 4) and each individual has 2 copies, one on each chromosome. There are six genotypes (2/2, 2/3, 2/4, 3/3, 3 /4, and 4/4) existing in three main isoforms: APOE2, APOE3, and APOE4[27][28]. Individuals with homozygous 4 allele have increased risk of developing AD, while

homozygous 2 is reported to be protective among the Caucasians. APOE is linked with cholesterol transport in the brain and amyloid deposition, and is a potential disease biomarker. Our preliminary analysis for any association between APOE 4 allele in 17 of the 28 prevalent Ibadan cases vs. 39 dementia-free controls revealed no association between APOE 4 allele and AD in elderly Nigerians[29]. Although high frequency of the 4 allele was documented in African populations, no association with AD was reported as at that time. That was the last study BOO participated in before he passed on.

Dementia Studies in Ibadan: 1995 and beyond

The next phase was to determine the incidence of dementia in the two cohorts since prevalence estimates are affected by disease duration and the number of new cases diagnosed. The biennial cycle of assessments made possible the derivation of incidence rates. Because of attrition at both sites and to ensure adequate number of participants for statistically credible analysis, cohort enrichment of participants aged 70 years and above (1892 in Indianapolis and 1939 in Ibadan) took place in 2001. Overall, a total of 4104 African Americans and 4433 Yoruba participants were studied for a total duration of 19 years (7 longitudinal evaluations). The respective incidence rates of dementia and AD were significantly lower among Yoruba (1.35% and 1.15%) than among African Americans (3.24% and 2.52%)[30]. The lower incidence rates in the Yoruba agreed with the initial observation of lower disease burden.

Apart from incidence, disease duration is another variable that can be responsible for low prevalence, and we determined the mortality rates. Analysis of 5-year data showed that dementia diagnosis was associated with increased mortality in both cohorts (Relative risk of dying in Idikan was 2.83 vs. 2.05 in Indianapolis)[31]. It was thus concluded that the impact of dementia on mortality risk may be similar for low-income and high-income countries. In addition, excess mortality could not be adduced as a sole reason for the lower prevalence estimate in the Yoruba cohort.

The Ibadan Study of Aging (ISA) utilized a multi-stage, stratified, clustered sampling of households in the Yoruba-speaking areas of Nigeria, encompassing eight contiguous states in the south-western and north-central regions of Nigeria. The main objective of this study was to describe the pattern of chronic diseases in older Nigerians and the associated disability. Two thousand one hundred and fifty-two individuals aged 65 years and older were enrolled between November 2003 and August 2004. Unlike the Indianapolis-Ibadan Study, ISA used a one-stage design, and the 10-word Delay Recall Test was deployed for assessing cognition. The prevalence estimate of probable dementia was 10.1% (95% CI, 8.6-11.8).[32] The study also reported lower quality of life in individuals diagnosed with probable dementia. The ISA study covered a much wider geographic area than the Indianapolis-Ibadan Study, and apart from the differences in study methodology, it raised the possibility of varying disease risk in the study area as well.

The ISA incidence study took place 39 months later and reported a rate of 21.85 per 1000 person years (2.2%), which though higher than that of the Indianapolis-Ibadan study, was lower than figures from other regions of the world. Indices of social isolation and cognitive reserve were reported to increase the risk of incident dementia[33].

The third Ibadan study on the burden of dementia was titled: "The Identification and Intervention for Dementia in Elderly Africans" (IDEA study). This was a collaboration between Newcastle University, Northumbria HealthCare Trust, UK, Kilimanjaro Christian Medical College, Hai and University of Ibadan. The study was funded by the Grand Challenges Canada (2013-2019) and had two main objectives: to develop a short and easy cognitive screening tool (CST) for early identification of dementia cases at the community level, and to evaluate a cost-effective treatment for dementia by way of cognitive stimulation therapy. The justification was the low rate of recognition of cases by primary health care practitioners. Their utilization would contribute to task shifting and remove the possible bias of concealment within communities. The lack of cost-effective therapy was the justification for trying CST since treatment costs were prohibitive and drug side effects were of concern.

The IDEA study intended to achieve the incorporation of dementia risk reduction approaches into existing chronic disease prevention strategies at primary care level, while identifying, documenting and promoting functional referral pathways. In addition, there were plans to develop key simple dementia-related messages for health workers and

care givers in the communities for effective sustenance of the research findings. Expectedly, advocacy and policy changes would be needed to accomplish these goals.

The IDEA cognitive screening tool was derived from the CSID and could be administered within 5 minutes. It was validated in 121 participants with very satisfactory psychometric properties[29]. It also had good inter-rater reliability and intra-class correlation coefficient, ranging from 0.74 to 0.79. In regression models, the cognitive screen was not affected by educational attainment[34]. This has now been developed into a computer app for use in field studies.

The prevalence study utilized a 2-stage design, and was carried out in Lalupon, a town located some 20 miles north of Ibadan city. Six hundred and forty-two participants were enrolled. One hundred and forty-two of them (22.1%) were diagnosed as cognitively impaired, including 2.9% with dementia[35]. Regression analysis showed that impaired recall and long-term memory deficit were independently associated with dementia.

Prevalence data on dementia in Africa is currently available from over a dozen studies as listed in table 2.36-49. Some variations are evident within countries and between regions of the world. With regards to incidence data, the Epidemiology of Dementia in Central Africa (EPIDEMCA) programme reported an incidence rate of 2.38%[50]. The higher mortality of dementia cases compared with non-demented age-matched controls was confirmed in the ISA and EPIDEMCA studies. Ojagbemi and colleagues carried out meta-analysis of published prevalence and incidence

estimates from studies in SSA. They reported pooled rates of 5% and 2% respectively from 5,200 cohort years.[49] The incidence data confirmed relatively lower incidence in SSA, and it would be essential to explore protective factors, either environmental or genetic, in later studies.

Table 2. Prevalence estimates of Dementia in Africa

Authors (Ref)	Study site	Sample size	Prevalence (%)	Comments
Hendrie HC et al. (25)	Ibadan, Nigeria	2494	2.29	CSID; DSM III
Farraq AF et al. (36)	Assuit, Egypt	2000	4.5	MMSE; DSM III; 60 years
Ochayi B & Thacher M (37)	Jos, Nigeria	280	6.4	CSID 1 Stage
Gureje O et al (32)	Southwest Nigeria	2152	10.1	10-word recall +ADL; DSM IV
Guerchet M et al. (38)	Djija, Benin Rep	514	2.6	CSID; 5-word test, DSM IV
Mbalesso HN et al. (39)	Bangui, CAR	496	8.1	CSID 5-word test; DSM IV
Guerchet M et al (40)	Congo	520	6.7	CSID, 5-word test, DSM IV
Yussuf AJ et al (41)	Zaria, Nigeria	322	2.79	CSID DSM IV
Paraisso MN et al. (42)	Cotonou	N/A	3.7	CSID, 5WT, 65 years Urban
El Thallawy HN et al (43)	Al Qusser, Egypt	8173	2.01	50 years; MMSE, DSM IVTR
Longdon AR et al (44)	Tanzania	1198	6.4	70 years+; CSID DSM IV
Ogunniyi A et al (35)	Lalupon, Nigeria	613	2.9	65 years, CSID, DSM IV
Khedr E et al. (45)	Qena, Egypt	691	5.07	60 years, CSID
De Jager CA et al (46)	Cape Town, SA	1394	11	CSID, One-stage study
Adeloye D et al (13)	Nigeria	9 studies	4.9%	Computer modelling, meta-analysis
Ojagbemi A et al (49)	Sub-Saharan Africa	44 studies	5%	Systematic Review

CSID – Community Screening Interview for Dementia; DSM – Diagnostic and Statistical Manual; 5WT – Five-word test; MMSE – Mini-Mental State Examination; ADL – Activities of Daily Living

Neuropsychiatric Manifestations of Dementia

Baiyewu studied in details the pattern of important behavioural and psychological symptoms of dementia in the Yoruba cohort of Idikan utilizing the Neuropsychiatric Inventory. Caregivers expressed their distress with the following: appetite change, night-time behaviour, disinhibition and aberrant motor behaviour. However, family members were less irritated by delusions and hallucinations, which could be stigmatizing[51].

Risk Factors for Dementia and AD

There is no cure for the degenerative dementias at the present time. Therefore, disease prevention should be of priority concern and should be based on the risk factors identified. A risk factor is any condition or biological variable that increases the risk of developing a disease. It is not causal but an association. The following are the documented risk factors for dementia and AD.

- **Sociodemographic risk factors**

Age is universally regarded as the most important risk factor for dementia, and this has been reported in virtually all studies, including the Indianapolis-Ibadan group, ISA and IDEA[7,8,32-35,52]. In Ojagbemi's meta-analysis of incident dementia cases in SSA, low educational attainment and poor pre-dementia cognitive functioning at baseline were shown to be important[49]. Female gender was reported in some studies, Indianapolis-Ibadan and ISA studies inclusive[32,52], to be associated with increased risk of dementia and this has been ascribed to their longer lifespan, since age is a dominant

risk factor. However, more recent studies are unravelling new biological underpinnings, including hormonal and genetic factors. Social isolation appeared to be a risk factor in the Yoruba, as "living with others" was protective. Yussuf and colleagues reported[53] that lack of spousal relationship in old age was associated with dementia. This also supported the view that social isolation is not advisable as individuals get older. **The engagement of older persons in communal and religious/social activities is therefore recommended as a way of boosting cognitive reserve and preventing dementia.**

- **Cardiovascular disease biomarkers**

The higher frequency of vascular factors in the African American cohort than in the Yoruba, namely: high blood pressure, diabetes mellitus, stroke, cholesterol, smoking and anthropometric measurements pointed to vascular aetiology, which was probably related to differences in their diets. The frequency of metabolic syndrome in the African American cohort was 27% as against 7% for the Yoruba. Twenty-four hour dietary recall revealed that the Yoruba diet was low in fat and high in carbohydrate (78% carbohydrates, 10% fat and 12% protein; for African Americans, the respective values were 52%, 34% and 15%)[54].

The Biomarkers Definitions Working Group of the National Institutes of Health defined a biomarker as ''a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic

intervention''[55]. Biomarkers serve as markers of disease processes and the following were assayed in the African Americans and Yoruba cohorts for cardiovascular diseases: E-selectin and plasminogen activator inhibitor 1 (PAI-1) for endothelial dysfunction, homeostasis model assessment (HOMA-IR for insulin resistance and index of metabolic syndrome), C-reactive protein and 8-isoprostane for oxidative stress/inflammation and homocysteine as an independent risk marker for ischaemic heart disease. Lastly, fasting lipid profiles were compared. Significant differences were found for lipid levels and insulin resistance. An attempt to tease out any possible pathogenetic mechanism underlying the differences in rates showed that there were no consistent changes with respect to endothelial dysfunction, measures of oxidative stress and inflammation. Homocysteine levels were not different between the cohorts[56] as shown in table 3.

Table 3. Cardiovascular biomarker comparison between African Americans and Yoruba

Mechanism	Test	AA	Yoruba	P - value
Endothdelial Dys.	E - selectin	44.5 (23.6)	37.9 (34)	<0.001
	PAI-1	21.9 (27.5)	39.5 (31.9)	0.9
	Homocysteine	17.4 (6.9)	8.1(18.9)	<0.001
Oxidation	CRP	14.81 (26.6)	8.1 (18.9)	<0.001
	8-Isoprostane	586.3 (1283)	1270.3 (1585.5)	<0.001
Insulin Res.	Metabolic Synd.	27%	7%	
	HOMA-IR	7.16	0.91	<0.001

Mechanism	Test	AA	Yoruba	P - value
Atherogenesis	Cholesterol	188.5 (38.6)	174.7 (40.9)	<0.001
	Triglycerides	104.7 (47)	89.5 (36.4)	<0.001
DNA Synthesis	Folate	9.81 (8.4)	5.87 (6.7)	<0.001
	Vit B12	612.6 (352.7)	785.5 (310.2)	<0.001

Source: Deeg M. et al, 2008.

PAI-1: Plasminogen Activator Inhibitor-1, CRP: C-Reactive Protein, HOMA-IR: Homeostatis Model Assessment, AA: African Americans

- **Association of apolipoprotein E and AD**

The association of APOE 4 allele with AD was investigated sequentially in the Indianapolis-Ibadan cohorts, as the number of participants studied and clinically-diagnosed AD cases increased. An interaction was observed between AD and rising cholesterol levels in both African Americans and Yoruba in individuals who did not possess the 4 allele, although there was no association of APOE and AD in the Yoruba[57-59]. However, over time and with more individuals diagnosed with dementia, a significant association was found between the possession of homozygous 4 allele and the development of AD in the Yoruba, but not in individuals with a single copy of the E4 allele[60]. The whole APOE saga and the eventual association with AD in the Yoruba could be considered as a slippery slope in dementia epidemiology. In African Americans, there was an association of AD with both the double and single copy of the 4 allele, even though the strength of association was lower than in Caucasians.

One major contribution of the Indianapolis-Ibadan study worth mentioning was the discovery of the fourth apolipoprotein E allele (labelled APOE1yoruba)[61]. This was found in a 70-year-old female individual whose direct sequencing showed homozygosity (C) at codon 112, and heterozygosity (C/T) at codon 158. That individual had one APOE4 allele and an APOE1y allele. The clinical implication of the APOE1y allele could be a subject of later studies.

- **Hypertension**

Hypertension is a risk factor for chronic cardiovascular disease and a silent killer. It predisposes to stroke, damages blood vessels and affects many target organs that work to maintain brain functioning like the kidneys and the heart. Both mid-life and late-life hypertension are associated with cognitive dysfunction. From 1997, blood pressure values were obtained consistently in all the study participants and used to predict the development of incident dementia 10 years later. The frequency of hypertension (BP > 140/90 mm Hg) was lower (60%) in those with normal cognition than in those diagnosed with dementia (70%). Multivariate analysis showed that the presence of hypertension increased the risk of dementia by 52%. Both systolic (Odds ratio 1.09 95% CI 1.03-1.16) and diastolic blood pressure (OR 1.22 95% CI 1.07 – 1.38) independently increased dementia risk as well as elevated mean arterial blood pressure (OR = 1.10 95% CI 1.01-1.21)[62]. Therefore, maintaining blood pressure within normal range would be advisable in old age as one of the ways of preventing dementia.

- **Lancet Commission on Dementia**

The Lancet Commission on prevention, intervention and care of dementia comprised experts drawn from all over the world. Their task was to utilize emerging information on disease epidemiology and carry out meta-analysis on available data to provide harmonized risk factors for dementia. The first report of the commission was published in 2017, and 9 dominant factors for dementia were identified. These were: less education in early life (< 15 years), hypertension, obesity, hearing loss in mid-life (45-64 years of age), while smoking, depression, physical inactivity, social isolation, and diabetes mellitus were dominant in later life (>65 years)[63]. The Lancet report recommended the following 3 approaches for preventing dementia:

- increasing cognitive reserve through education, social networking and improved hearing;
- reducing vascular, oxidative and neurotoxic brain damage through the treatment of chronic vascular diseases, healthy diet, reduced smoking etc.; and
- reducing brain inflammation by dietary regulation and use of non-steroidal anti-inflammatory drugs as appropriate.

The commission was expanded in 2019 to include 2 experts from low-and middle-income countries (Dr. Amit Dias from India and myself). The 2020 publication is the current world reference on the dominant risk factors for dementia, and 3 new factors were added to the previous nine. These are: traumatic brain injury, air pollution and excessive alcohol

consumption[64]. The ISA study had shown that lifetime history of alcohol use was a significant risk factor for later dementia[33]. The report concluded that about 40% of dementia cases can be prevented through concerted global efforts directed at the identified risk factors. This should be welcome news for those involved with caring for older persons in low- and middle-income countries, where the number of dementia cases is increasing rapidly. Data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGERS) had shown that multi-domain lifestyle-based intervention consisting of diet, exercise, cognitive stimulation and monitoring of vascular morbidities could reduce the risk of cognitive and functional impairment among at-risk persons[65]. The high-income countries are better placed with regards to battling air pollution, since they use less fossil fuels and have embarked on cleaner energy sources. The low- and middle-income countries will need to emulate this practice.

A decline in the prevalence and incidence rates of dementia was observed in many studies in Europe and America about a decade ago[66]. The reasons adduced were higher education and better management of vascular factors, including stroke reduction. Even among African Americans in the Indianapolis-Ibadan Study, a reduction in dementia incidence was reported over a 10-year period of study[67]. Shrijvers and colleagues carried out a longitudinal magnetic resonance imaging study that compared brain sizes of cognitively-normal persons in 1995–1996 against images obtained in 2005–6. They reported larger brain volumes and

less extensive cerebral small-vessel disease[68]. It is therefore expedient to pay attention to preventive strategies as the best approach for preventing a possible dementia epidemic globally.

New risk factors keep emerging and the recent ones (as at December 22, 2021) are resting heart rate and cataract surgery. This highlights the importance of cardiovascular health in keeping the brain functioning well, while improved vision in the elderly could suggest better social contacts and benefits from visual cues. More risk factors will come up for consideration by the time the Lancet Commission on Dementia convenes again.

- **Body Mass Index as an Indicator of Cognitive Dysfunction**

Weight loss is common as individuals advance in age and this can be explained by reduced dietary intake because of reduced activities in general. Individuals with neurodegenerative diseases, in particular, are at risk of weight loss due to forgetfulness to eat and loss of special senses needed to appreciate food, like the sense of smell and taste *(not due to COVID-19 infection)*. Prospective BMI measurements of Idikan participants revealed that over a 10-year period, older persons with normal cognitive abilities had no appreciable change in their BMI readings, while those who developed dementia had progressive reduction at a rate of 0.19 $kg/m^2/year$[69]. Therefore, when elderly persons lose weight for no obvious reasons, it may be worthwhile to think of dementia or other neurodegenerative diseases setting in,

and appropriate tests organized to diagnose the problem early.

- **Genome-Wide Association Studies of Dementia and the Search for an African Dementia Gene**

Genome-Wide Association Study (GWAS) is a research approach for associating specific genetic variations with particular diseases through scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease[70]. This approach was used to study genetic materials obtained from the Indianapolis-Ibadan cohort, with a view to discovering a possible African dementia gene. Hitherto, most of the genetic information available came from studies on Caucasians.

In the African American cohort, early onset AD was associated with two variants (rs3752246 and 4147929) in the adenosine triphosphate-binding cassette subfamily A member 7 (ABCA7) gene, but these variants were not observed in the Yoruba cohort, who instead had one variant (rs9331949) in the clusterin gene (CLU) and two variants (rs10498033 and 12881735) in the solute carrier family 24-member 4 gene (SLC24A4). The association even appeared to be stronger for triglyceride levels than for APOE *(Hendrie H, unpublished observation)*. The implication of these results awaits further analysis and definitely more research. The preliminary conclusion at the moment is that although both African Americans and Yoruba are of African ancestry, different genes seem to be associated with AD risk. One area of interest is the influence of physical activity on underlying

genetic inheritance. Dr. Mark Gluck, Director, Aging and Brain Health Alliance, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, USA has reported a link between two variants of the ABCA7 gene and aerobic fitness[71]. This would an exciting area for further studies.

Cost-Effective Management of Dementia

Availability of effective medications for symptomatic treatment of dementia is a challenge facing family members when caring for their loved ones with the disease. Prohibitive costs and lack of disease-modifying therapy are major concerns. In an attempt to solve the problem of effective treatment options, the IDEA study deployed an adaptation of cognitive stimulation therapy (CST) developed by Spector and Orrell[72]. It is a form of group-based, reminiscent, psychological and social treatment, aimed at improving function and slowing deterioration. It had been used in various cultures with success. It is administered in 14 sessions over 7 weeks and makes task-shifting in the care of dementia patients possible because it is usually delivered by trained, non-specialist health workers. The test items were carefully selected and harmonized for participants in Lalupon and Hai District of Tanzania. Unfortunately, only 9 of the 12 eligible participants completed the 7-week treatment in the preliminary study at Lalupon as against 34 participants in Hai[73,74]. The preliminary results showed that CST led to improvement in language functioning and praxis, i.e., the ability to perform previously learned motor tasks of participants so treated. There was significant reduction in

caregiver burden which was assessed using the Zarit Caregiver Burden scale and there were fewer neuropsychological distressing symptoms. Data from Hai District showed that CST performed as well as prescribing an acetylcholinesterase inhibitor for the cases[74]. CST was therefore considered as a useful addition to the management of mild to moderate dementia cases in LMICs.

Some Recent Advances in Cognitive Neuroscience

Cognitive neuroscience, described as the last frontier of man, has witnessed giant strides in understanding the complexities in the pathogenesis of dementia, updating disease phenotypes for more accurate classification of cases and in therapeutic interventions. BOO had noted in one of his numerous lectures that advances in science were taking place with such rapidity that the only way to keep pace would be to run (sic read) as fast as one could to avoid being left behind[75]. However, researchers in developing countries have been forced to rely solely on advances in science and giant strides in technological development from western countries. It is analogous to a situation of watching things happen rather than making things happen, an unfortunate development in science.

- **Changing Diagnostic Criteria - Endophenotyping of Dementia**

The diagnosis of dementia has moved beyond being based entirely on clinical criteria. Substantial errors have been reported in up to a third of the cases if only core clinical features are used. Secondly, the blurry aspect of prodromal

dementia has become better defined with the use of biomarkers in making early diagnosis with better precision. It has been reported that the deposition of abnormal proteins in the brain precedes clinical symptomatology by up to two decades[76-78]. Modern dementia classification now entails the combination of clinical features with neuroimaging findings and biomarker results. Structural and functional imaging is done with either magnetic resonance imaging or 18F-fluoro deoxy glucose positron emission tomography (18F-FDG–PET). In-vivo amyloid imaging is now possible using 11C-labelled Pittsburgh compound B or 18F-labelled tracers (florbetapir, flutemetamol and florbetaben PETs).

The biological disease markers (Aβ42, phosphorylated tau, total tau and neurofilament light) are assayed in the cerebrospinal fluid or plasma[76-78]. The first abnormal biomarker in AD is Aβ42 with cerebrospinal fluid (CSF) levels falling usually when the affected individual is still asymptomatic, followed by an increase in total tau/phosphorylated tau (τP-181) levels. CSF biomarkers have now been incorporated in the diagnostic criteria for AD because of their high sensitivities and specificities approaching 90%. The major drawback is the challenge of carrying out lumbar puncture in older persons for obtaining CSF for these measurements. Therefore, plasma levels of phosphorylated tau (P-tau) isoforms, i.e., tau phosphorylated at 181 (P-tau181) and 217 (P-tau217), are increasingly being used since they have high concordance with amyloid PET and their levels also reflect the degree of cognitive impairment[55,76-80]. Neurofilament light (NfL) elevation can

also be predictive of cognitive impairment. Alpha-synuclein is the biomarker for LBD and TAR-DNA binding protein-43 (TDP-43) for FTLD.

Currently, AD is diagnosed where there is reduced amyloid load in biological fluid with elevated tau combined with brain atrophy in magnetic resonance imaging/PET. With the use of biomarkers and imaging data, AD is now classified into preclinical, prodromal and AD dementia. Preclinical stage implies the presence of biomarker abnormalities without clinical features. Prodromal AD has biomarker abnormalities and memory symptoms but no functional impairment. For definite AD diagnosis, histopathological evidence from brain biopsy or autopsy and genetic evidence of mutation on chromosome 1, 14, or 21 must be available along with the classical course of progressive memory deficit[55,76-80].

The National Institute of Aging and Alzheimer's Association (NIA–AA) Research Framework group also introduced the AT(N) system for deciding on the contributions of biomarkers towards making a diagnosis of probable AD[81-83]. A stands for amyloid load (Aβ42 or Aβ42/A40, T for tau accumulation and tangle formation (phosphorylated tau P-181 or total tau) and N for neurodegeneration (neuronal or axonal loss demonstrated by PET). The profile of AD is presented as A+T+(N+), whilst A+T+(N) would imply the presence of AD pathological substrate before degeneration has set in. Normal levels of all three biomarkers implies absence of AD. Profiles such as A+ but normal value of either T or N (T (N) or T (N)+) would

suggest Alzheimer's pathological change (change from normal with the acquisition of amyloid biochemistry/pathology). Although the AT(N) system was designed mainly for research purposes, it can be used in clinical practice in cases of atypical presentations and/or unusual clinical course. Errors can occur when cases with non-amnestic AD or those presenting first with primary language problems mimicking FTLD are encountered. Other mimics are: primary cortical atrophy presenting like Balint's syndrome, mixed AD and VD, Lewy body disease (LBD), corticobasal ganglionic degeneration and normal-pressure hydrocephalus, which usually manifests as a combination of incontinence, memory impairment and gait apraxia.

Biomarkers are not without their drawbacks which include imperfection in their utility in the diagnosis of AD,[81-84] as shown in table 4. Their utility also diminishes with age (after 70 years). Other problems include additional cost of the procedure, quality control issues and low specificity in some instances. For example, low Aβ42 level is also found in LBD, VD and cerebral amyloid angiopathy. Elevated CSF total tau can occur following head trauma, stroke and Creutzfeldt-Jakob disease. Thus, the diagnosis of AD using biomarkers is not sacrosanct and reliance on clinical judgment is still very important. Moreover, testing for biomarkers is not readily available in many low- and middle-income countries (LMICs). More limited is the availability of PET facilities for demonstration of amyloid etc., even in high income countries where it is more of a research tool. Although single photon emission computerized tomography (SPECT) is more widely

available and cheaper than PET, it has not been included in the diagnostic criteria because of its lower precision (sensitivity < 80% and specificity 65 – 93%). The possibility of many false positive and false negative cases will make any clinician wary of deploying such technology with the high potential of misclassifying cases. The lack of these facilities in many LMICs is a hindrance to high-impact research in such countries, and indeed is a contemporary challenge for being competitive in winning grants. In my view, the best way out is for researchers in LMICs to collaborate with those in HICs where these facilities exist, so as not to be left out.

Table 4. Sensitivity and specificity of biomarkers for AD diagnosis (Ref. 82,83)

Ptau/Aβ42	Sensitivity (%)	Specificity (%)
Diagnosis of AD	91.6	85.7
AD vs. Bv FTLD	91.7	98.3 AD
AD vs. Semantic Dementia	**92.6**	**84.2**

Bv FTLD – Behavioural variant of FTLD, AD = Alzheimer's disease

Causes of Low β42:	**Elevated Total Tau**
Lewy Body Dementia	**Head trauma**
Vascular Dementia	**Stroke**
Cerebral amyloid angiopathy	**Creutzfeldt-Jakob disease**

- **Retinal Imaging of Amyloid**

The eye is the window to the brain and consequently brain pathology should be visible in the eye. This is the basis of the recent attempt to demonstrate the presence of amyloid in the retina, as a surrogate for amyloid deposition in the brain, using optical coherence tomography (OCT). Recent studies of

carriers of familial Alzheimer's disease gene who are cognitively normal showed the presence of amyloid in their retina using OCT[85]. Therefore, OCT findings may be useful as surrogate for detecting amyloid in the brain prior to the onset of cognitive decline.

- **Disease-Modifying Treatment for Dementia – Aducanumab**

Immunotherapy against amyloid was first attempted by Dale Schenk about two decades ago as a disease-modifying strategy. The trial involved using antibodies against amyloid in a mouse model of AD[86]. Unfortunately, the development of encephalitis limited the potential of that innovative therapy. Since then, the search for the ideal treatment has continued on many fronts based on various pathogenetic targets with lots of disappointment along the way. Passive immunotherapies were tried and anti-amyloid vaccine (CAD 106) is in Phase III trial stage. Refinement of the strategy of using antibodies against amyloid in the brain led to the trials of Solazenumab, Crenezumab, Gantenerumab and Aducanumab. Other strategies include inhibition of Beta Amyloid Clearing Enzyme (BACE) and tau-based therapies, comprising antibodies, active immunization, anti-aggregants, tau kinase inhibitors and gene therapy[87].

Aducanumab, an amyloid-targeting monoclonal antibody, is the first drug that has been approved for the treatment of AD. The approval was announced by the Food and Drug Administration, US on June 7, 2021[88]. Aducanumab, marketed by Biogen as *Aduhelm*, is delivered

by intravenous infusion over one hour and repeated after 21 days in incremental doses, starting from 1 mg/kg and progressively increasing to 10 mg/kg, diluted with normal saline. The approval of a disease-modifying therapy for AD represents a landmark achievement in the treatment of dementias. The cost is however prohibitive (initially above $50,000:00 per person annually but the amount was reduced by about 50% on December 19, 2021). The requirements before administration are also cumbersome. These include availability of expert clinicians skilled in the recognition of early AD, facilities for amyloid PET and MRI, lumbar puncture capability, as well as experts in the recognition and management of amyloid-related imaging abnormalities and for genetic counselling[89]. Therefore, practitioners in LMICs are disadvantaged in many ways as their patients with dementia cannot benefit from such disease-modifying therapy for now. We can only imagine its benefits without being active research investigators in any clinical trial of such an agent. This is one of the challenges of contemporary relevance.

- **the Place of Assistive Technology in Management**

The burden of care of patients with dementia is borne by the caregiver, who are either relatives or paid caregivers. Most of the care is provided at home because institutionalized care is not only frowned at, but such homes are also not readily available. Therefore, easing the burden on caregivers can improve their quality of life, allowing some freedom for both the patient and the caregivers without exposing them to

danger. Technological advancements with wearable, simple devices, telemedicine are available for the management of individuals with dementia, while the application of artificial intelligence in diagnosis is being explored. Available devices include alarms for voiding, teleprompters for eating, using medications, etc., alarms on doorways or those worn by the patient to alert the caregiver in cases of wandering away. Their use has even become more important with the COVID-19 pandemic, where lockdowns, social distancing and wearing of masks add to the isolation and psychological burden of individuals with dementia.

What is the Way Out of the Problem of Dementia in LMICs?

The challenges of dementia in SSA can be summarized as follows: increasing number of people with dementia, stigmatization, diagnostic delays due to limited resources, lack of awareness, poor access to healthcare and its attendant high cost. Technological limitation constitutes a hindrance to progress in LMICs and this affects creativity, though bright ideas may not be lacking. An international consortium drew up an action plan for combatting the challenges of dementia on a global scale[90]. The key points are: the identification and reduction of the risk factors, fund allocation for dementia research and care, improving quality of life of individuals with dementia (reducing stigma), capacity building involving health care workers, teachers and others to manage dementia crisis, and supportive living environments.

For the future, a 3-prong approach involving a combination of increased awareness, personalized care and deployment of technology holds the key for optimal care in LMICs. Increased awareness through health education, organized campaigns and distribution of information leaflets is a necessary first step. Information is key because it takes away misconceptions about the disease, informs about care opportunities, and leads ultimately to the generation of data that can be used for planning purposes. Individualized care is advocated as being necessary for identifying the peculiar needs of dementia patient since one size does not fit all in care provision. This hinges on joint decision-making about care and holistic needs assessment that would involve the patients and family members, while also empowering non-specialists (e.g., in rural settings) to perform comprehensive assessment. This is the basis of personalized care. However, it continues to be debated whether the best approach is individualized care or a population-based approach that can target many neurodegenerative diseases at the same time rather than dementia alone.[91,92] The jury is out on that issue. Due to the low literacy rate in SSA, more culturally-appropriate cognitive assessment tools for measuring mental capacity need to be developed or the currently available ones improved upon. Lastly, culturally-appropriate and cost-effective technology-driven care should be adopted and tailored to individual needs. Digital biomarkers in the form of wearable kits will be needed for collecting Alzheimer's-specific metrics, using such tools as actigraphy and simple computer apps[93,94]. The data obtained can be analyzed

remotely by specialists while circumventing heavy patient load and other burden on the healthcare systems. This may be a potential solution for combatting manpower shortages in LMICs. Attempts were made to achieve some of these measures in the IDEA study – development of computer app for the short, validated, culturally-appropriate IDEA cognitive screen, empowerment of primary health care workers and use of cognitive stimulation therapy. There is a need for biomedical engineers to design simple, wearable kits that can be used for monitoring individuals with dementia. Collaboration is the key word for all these to happen and for maximal benefit to all stakeholders.

Conclusion

The challenges of dementia and Alzheimer's disease as presented in this lecture are universal and demand a collective approach. The goals of the Ibadan Dementia Research Studies have been met through the derivation of credible data on disease burden and the identification of some unique risk factors, including apolipoprotein E. In addition, cognitive stimulation therapy was demonstrated to be an affordable treatment strategy. Prevention should utilize tailored, multidomain approaches that simultaneously target many risk factors at both individual and population level. A lot still needs to be done, including gene identification and use of biomarkers in phenotyping our cases. Of note is the African Dementia Consortium[95] being assembled by Dr. Rufus Akinyemi, which should take dementia research to the next stage.

Closing Remarks:

BOO will forever be remembered as the pioneer of neuroepidemiology in Africa, whose vision led to the ground-breaking findings from the dementia studies that have kept Ibadan relevant in international circuits. I have endeavoured to highlight the key contributions by Ibadan researchers in this memorial lecture. Professor Hugh Hendrie noted in the second of these memorial lecture series that Professor Osuntokun's creativity, influence and persistence significantly contributed to the Indianapolis-Ibadan study coming to fruition. In addition, he left with us his unique attributes of excellence, dedication and scientific integrity, because excellence mattered to him more than success. Every year, this lecture series provides us the unique opportunity of appreciating the wide breadth of BOO's contributions to the world of neuroscience. We, his mentees and successors, face the daunting challenge of emulating his chequered academic career and his penchant for excellence. Professor Osuntokun will continue to live in our hearts and he will never be forgotten.

Acknowledgements

I thank Professor Olabopo Osuntokun and all members of the BOT Osuntokun Trust for this opportunity to present our modest contributions in dementia research and for these annual memorial lectures. I thank all the study participants of the various studies who provided us with the data and for their time. I appreciate Professor T.A. Junaid for the initial neuropathological studies and for his support. I sincerely

appreciate all members of the Indianapolis-Ibadan Dementia Study (especially Professors Hugh Hendrie, Kathleen Hall, ABOO Oyediran, Oye Gureje, Segun Baiyewu, Fred Unverzagt, Su Gao and EA Bamgboye) and the IDEA team (Professors Richard Walker, Catherine Dotchin, Declare Mushi, Dr. Pelumi Adebiyi, Olaide Olakehinde, Akeem Siwoku and Dr. Tunde Adediran), Drs. Akin Ojagbemi and Rufus Akinyemi for providing excellent materials for this overview of dementia. I appreciate Prof. Rhoda Au and Philip Joung of Boston University for the supply of useful materials related to Davos Alzheimer Cooperative Initiatives. Finally, I thank the funding agencies – National Institute of Aging, NIH, USA, Grand Challenges Canada. I acknowledge Drs Rufus Akinyemi, Samuel Ajayi and Akintomiwa Makanjuola for their excellent editorial reviews. I thank Victor Ogaji for his technical support.

References

1. Cambridge Advanced Learner's Dictionary. Cambridge University Press, 2003
2. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization, 1992.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth edition (DSM-5). Arlington, VA: American Psychiatric Association, 2013.
4. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and Alzheimer's disease. *Archives of Medical Research* 2012; 43: 600 -608.

5. Ogunniyi A, Akang EEU, Gureje O et al. Dementia with Lewy Bodies in a Nigerian: A case report. *Int Psychogeriatr* 2002, 14: 211-218.
6. Akinyemi RO, Owolabi MO, Makanjuola VA, Ogunseyinde AO, Ogunniyi A. Frontotemporal dementia in a Nigerian woman: Case report and brief review of the literature. *Afr J Med Med Sci* 2009;38: 71-75.
7. Amoo G, Akinyemi RO, Onofa LU, et al. Profile of clinically-diagnosed dementias in a neuropsychiatric practice in Abeokuta, south-western Nigeria. *Afr J Psychiatry (Johann)* 2011; 14(5): 377-82.
8. Akinyemi RO, Allan L, Owolabi MO, et al. Profile and determinants of vascular cognitive impairment in African stroke survivors: The CogFAST Nigeria Study. *J Neurol Sci.* 2014; 346(1-2): 241-9.
9. Perkins GD. Disorders of higher cortical function. *J Neurol Neurosurg Psych* 1995; 416.
10. Osundare Niyi. Lifeline Snapsong 133. The Nation. July 18, 2021.
11. World Health Organisation. Dementia: A Public Health Priority. World Health Organisation. Geneva. 2012.
12. Alzheimer's Disease International. Dementia in sub-Saharan Africa : challenges and opportunities. ADI. September 2017. Ch 2.
13. Adeloye D, Auta A, Ezejimofor M, Oyedokun A, Harhay MO, Rudan I, Chan KY. Prevalence of dementia in Nigeria: A systematic review of the evidence. *J Glob Health Rep.* 2019 ; 3 .
14. United Nations. *World Population Ageing 2019*. New York.
15. Wimo A, Guerchet M, Alli GC, Wu et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheiner Dement* 2017; 13(1): 1–7.
16. Adebiyi AO, Fagbola MA, Olakehinde O, Ogunniyi A. Enacted and implied stigma for dementia in a community in south-west Nigeria. *Psychogeriatrics* 2015.
17. Nwakasi CC, de Medeiros K, Bosun-Arije FS. "We Are Doing These Things So That People Will Not Laugh at Us": Caregivers' Attitudes About Dementia and Caregiving in Nigeria. *Qual Health Res.* 2021; 31(8):1448-1458.
18. Henderson AS. The epidemiology of Alzheimer's disease. *Br Med Bull.* 1986; 42(1):3-10.

19. Ogunniyi A, Osuntokun BO, Lekwauwa UG. Screening for dementia in elderly Nigerians – Result of the pilot test of a new instrument. *East Afr Med. J.* 1991; 68(6): 448-454.
20. Osuntokun BO, Ogunniyi A, Akang EEU. Aghadiuno PU, Ilori A, Bamgboye EA, Beyreuther K, Masters C. bA4-amyloid in the brains of non-demented Nigerian Africans. *Lancet* 1994; 343: 56.
21. Ogeng'o JA, Cohen DL, Sayi JG, et al. Cerebral amyloid beta protein deposits and other Alzheimer lesions in non-demented elderly East Africans. *Brain Pathol.* 1996; 6(2): 101-7.
22. Osuntokun BO, Hendrie HC, Ogunniyi AO, et al. Cross-cultural transnational comparative geographical epidemiological studies of age-related dementias and etiological clues of Alzheimer's disease. *Ethnicity and Disease* 1992; 2(4): 352-357.
23. Hall KS, Ogunniyi AO, Hendrie HC, et al. A cross-cultural community-based study of dementias: methods and performance of the survey instrument – Indianapolis, USA and Ibadan, Nigeria. *Int. J Methods in Psychiatry Res.* 1996; 6: 129-142.
24. Baiyewu O, Unverzagt FW, Lane KA, et al. The Stick Design: A new measure of visuo-constructional ability. *J. Int. Neuropsych. Soc.* 2005; 11: 598-605.
25. Hendrie HC, Osuntokun BO, Hall KS, et al. Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *Am J Psychiatry* 1995; 152: 1485-1492.
26. Cooper RS, Kaufman JS. Race and hypertension: Science and nescience. *Hypertension* 1998; 32(5): 813-6.
27. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; 261: 921–923.
28. Belloy ME, Napolioni V, Greicius MD. A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward. *Neuron* 2019; 101(5): 820–838.
29. Osuntokun BO, Sahota A, Ogunniyi AO, et al. Lack of association between Apolipoprotein Eε4 allele and Alzheimer's disease in elderly Nigerians. *Ann Neurol* 1995; 38: 463-465.
30. Hendrie HC, Ogunniyi A, Hall KS, et al. Incidence of dementia and AD in two communities: Yoruba residing in Ibadan, Nigeria, and

African Americans residing in Indianapolis, USA. *JAMA* 2001; 285: 739-47.

31. Perkins AJ, Hui SL, Ogunniyi A, et al. Risk of mortality for dementia in a developing country: The Yoruba in Nigeria. *Int. J. Geriatr. Psychiatr.* 2002; 17: 566-573.
32. Gureje O, Ogunniyi A, Kola L. The profile and impact of probable dementia in a sub-Saharan African community: Results from the Ibadan Study of Aging. *J. Psychosom. Res.* 2006; 61(3): 327-333.
33. Gureje O, Ogunniyi A, Kola L, Abiona T. Incidence of and risk factors for dementia in the Ibadan study of aging. *J Am Geriatr Soc.* 2011; 59: 869–74.
34. Gray WK, Paddick SM, Collingwood C, et al. Community validation of the IDEA study cognitive screen in rural Tanzania. *Int J Geriatr Psychiatry* 2016; 31(11): 1199-1207.
35. Ogunniyi A, Adebiyi AO, Adediran AB, Olakehinde OO, Siwoku AA. Prevalence estimates of major neurocognitive disorders in a rural Nigerian community. *Brain Behav.* 2016; 6(7).
36. Farrag AF, Farwiz HM, Khedr EH, Mahfouz RM, Omran SM. Prevalence of Alzheimer's disease and other dementing disorders: Assuit-Upper Egypt study. *Dement Geriatr Cogn Disord.* 1998; 9: 323-328.
37. Ochayi B, Thacher TD. Risk factors for dementia in central Nigeria. *Aging Ment Health* 2006; 10: 616- 620.
38. Guerchet M, Houinato D, Paraiso MN. Cognitive impairment and dementia in elderly people living in rural Benin, West Africa. *Dementia and Geriatr Cognitive Disorders* 2009; 22: 34-41.
39. Mbelesso P, Tabo A, Guerchet M, Mouanga AM, et al. Epidemiology of dementia in elderly living in the 3rd borough of Bangui (Central African Republic). *Bull Soc Pathol Exot.* 2012; 105(5):388-95.
40. Guerchet M, M'belesso P, Mouanga AM, et al. Prevalence of dementia in elderly living in two cities of Central Africa: The EDAC survey. *Dement Geriatr Cogn Disord.* 2010; 30(3): 261-8.
41. Yusuf AJ, Baiyewu O, Sheikh TL, Shehu AU. Prevalence of dementia and dementia subtypes among community-dwelling elderly people in northern Nigeria. *Int Psychogeriatr.* 2011; 23(3): 379-86.

42. Paraïso MN, Guerchet M, Saizonou J, et al, Prevalence of dementia among elderly people living in Cotonou, an urban area of Benin (West Africa). *Neuroepidemiology* 2011; 36(4):245-51.
43. El-Tallawy, HM, Farghly MH, Badry R, et al. Prevalence of dementia in Al-Quseir city, Red Sea Governorate, Egypt. Clinical Interventions in Aging 2014; 9: 9–14.
44. Longdon AR, Paddick SM, Kisoli A, et al. The prevalence of dementia in rural Tanzania: A cross-sectional community-based study. *Int J Geriatr Psychiatry* 2013: 28(7):728-372.
45. Khedr E, Fawi G, Abbas MA, et al. Prevalence of mild cognitive impairment and dementia among the elderly population of Qena Governorate, Upper Egypt: A community-based study. *J Alzheimers Dis.* 2015; 45(1): 117–126.
46. de Jager CA, Msemburi W, Pepper K, Combrinck MI. Dementia prevalence in a rural region of South Africa: A cross-sectional community study. *Journal of Alzheimer's Disease* 2017; 1087–1096.
47. Olayinka OO, Mbuyi NN. Epidemiology of dementia among the elderly in sub-Saharan Africa. *Int. J Alz. Dis.* 2014.
48. George-Carey R, Adeloye D, Chan KY, et al. An estimate of the prevalence of dementia in Africa: A systematic analysis. *J Glob Health* 2012; 2(2).
49. Ojagbemi A, Okekunle AP, Babatunde O. Dominant and modifiable risk factors for dementia in sub-Saharan Africa: a systematic review and meta-analysis. *Frontiers Neurol* 2021; 12.
50. Samba H, Guerchet M, Bandzouzi BN, et al. Incidence of dementia among older adults in central Africa: First results from the Republic of Congo in the EPIDEMCA-FU study. *Alzheimers Dement* 2015;11:221–2.
51. Baiyewu O, Smith-Gamble V, Akinbiyi A, et al. Behavioral and caregiver reaction of dementia as measured by the neuropsychiatric inventory in Nigerian community residents. *Int. Psychogeriatr* 2003;15: 399-409
52. Hall KS, Gureje O, Gao S, Ogunniyi A, et al. Risk factors and Alzheimer's disease: A comparative study of two communities. *Aust. New Zealand J Psychiatry* 1998; 32: 698-706.

53. Yussuf AJ, Baiyewu O, Bakari AG, et al. Low education and lack of spousal relationship are associated with dementia in older adults with diabetes mellitus in Nigeria. Psychogeriatrcs 2018 ; 18(3) : 216-223
54. Ogunniyi A, Baiyewu O, Gureje O, et al. Epidemiology of dementia in Nigeria: Results from the Indianapolis-Ibadan Study. *Euro J. Neurol* 2000; 7: 485-490.
55. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement* 2011; 7(3).
56. Deeg M, Baiyewu O, Gao S, et al. A comparison of cardiovascular risk factor biomarkers in two populations: African Americans and Yoruba Nigerians. *Ethnicity & Disease* 2008; 18: 427-433.
57. Hall K, Murrell J, Ogunniyi A, et al. Cholesterol, APOE genotype and Alzheimer's disease: An epidemiological study of Nigerian Yoruba. *Neurology* 2006; 66: 223-227.
58. Murrell J, Price BM, Lane KA, et al. Association of Apolipoprotein E genotype and Alzheimer's disease in African Americans. *Arch. Neurol.* 2006; 63: 431-434.
59. Gureje O, Ogunniyi A, Baiyewu O, et al. APOE epsilon4 is not associated with Alzheimer's disease in elderly Nigerians. *Ann. Neurol.* 2006; 59(1): 182-185.
60. Hendrie HC, Murrell J, Baiyewu O, et al. APOE ε4 and the risk for Alzheimer's disease and cognitive decline in African Americans and Yoruba. *Int Psychogeriatr.* 2014; 26(6): 977-85.
61. Murrell JR, Price BM, Baiyewu O, et al. The fourth apolipoprotein E haplotype found in the Yoruba of Ibadan. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 2006; 141(4): 426-427.
62. Ogunniyi A, Lane KA, Baiyewu O, et al. Hypertension and incident dementia in community-dwelling elderly Yoruba Nigerians. *Acta Neurol Scand.* 2011; 124(6): 396-402.
63. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; 390: 2673–734.

64. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; 396(10248):413-446.
65. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimers Dement* 2013; 9: 657–65.
66. Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. *N Eng J Med* 2013; 369(24): 2275–2277.
67. Hall KS, Gao S, Baiyewu O, et al. Prevalence rates for dementia and Alzheimer's disease in African Americans: 1992 versus 2001. *Alzheimers Dement.* 2009; 5(3): 227-33.
68. Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology* 2012; 78(19): 1456-63.
69. Ogunniyi A, Gao S, Unverzagt FW, et al. Weight loss and incident dementia in elderly Yoruba Nigerians: A 10-year follow-up study. *Int Psychogeriatr*. 2010; 25: 1-8.
70. https://www.genome.gov/genetics-glossary (Accessed on November 1, 2021.
71. Sindha N, Berg CN, Shaw A, Gluck MA. ABCA7 genotype moderates the effect of aerobic exercise intervention on generalization of prior learning in healthy older African Americans. *J Alz Dis* 2020; 74: 309-18.
72. Spector, A., Orrell, M, Woods, B. Cognitive Stimulation Therapy (CST): effects on different areas of cognitive function for people with dementia. *Int J Geriatr Psychiatry* 2010; 25(12), 1253-1258.
73. Paddick SM, Mkenda S, Mbowe G, et al. Cognitive stimulation therapy as a sustainable intervention for dementia in sub-Saharan Africa: Feasibility and clinical efficacy using a stepped-wedge design. *Int Psychogeriatr.* 2017.
74. Olakehinde O, Adebiyi A, Siwoku A, et al. Managing dementia in rural Nigeria: Feasibility of cognitive stimulation therapy and exploration of clinical improvements. *Aging Ment Health* 2018: 1-5.

75. Osuntokun BO. Recent advances in neuroimaging: Relevance to neuropsychiatric practice in developing countries. Guest lecture 23rd Annual Conference of Radiologists of West Africa, Ilorin, 1985.
76. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: Current status and prospects for the future. *J Intern Medicine* 2018; 284: 643–663.
77. Sperling R, Johnson K. Biomarkers of Alzheimer Disease: Current and Future Applications to Diagnostic Criteria. *Continuum (Minneap Minn)* 2013; 19(2): 325–338.
78. Shaw LM, Korecka M, Clark CM, Lee VMY, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nature Reviews* 2007; 6: 296-303.
79. Schindler SE, Bateman RJ. Combining blood-based biomarkers to predict risk for Alzheimer's disease dementia. *Nature Aging* 2021; 1: 26–28.
80. Hampel H, Wilcock G, Andrieu S, et al. Biomarkers for Alzheimer's disease therapeutic trials. *Progress in Neurobiology*. 2011; 95: 579-593.
81. Paraskevas GP, Kapaki E. Cerebrospinal Fluid Biomarkers for Alzheimer's Disease in the Era of Disease-Modifying Treatments. *Brain Sci.* 2021; 11: 1258.
82 Henriksena K, O'Bryant SE, Hampel H, et al. The future of blood-based biomarkers for Alzheimer's disease. *Alzheimer's & Dementia* 2013;1–17.
83. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: Revising the NINCDS–ADRDA criteria. *Lancet Neurol* 2007; 6: 734–46.
84. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database of Systematic Reviews* 2017; 3.
85. Grayson W. Armstrong, et al. Retinal Imaging Findings in Carriers with PSEN1-Associated Early-Onset Familial Alzheimer Disease Before Onset of Cognitive Symptoms. *JAMA Ophthalmol.* 2021; 139(1):49-56.
86. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuate Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 1999; 400(6740): 173-7.

87. Mortada I, Farah R, Nabha S, et al. Immunotherapies for Neurodegenerative Diseases. *Front. Neurol.* 12.
88. Alexander GC, Knopman DS, Emerson SE, et al. Revisiting FDA Approval of Aducanumab. *N Eng J Med* 2021; 385; 769-771.
89. Cummings J. New approaches to symptomatic treatments for Alzheimer's disease. *Mol Neurodegener.* 2021; 16(1): 2.
90. Chertkow H. An Action Plan to Face the Challenge of Dementia: International Statement on Dementia from IAP for Health. *J Prev Alzheimer's Dis.* 2018; 5(3): 207-212.
91. Wallace L, Brayne C. The need for a better global dementia response. *Lancet Neurol.* 2021.
92. Seeher K, Cataldi R, Chowdhary N, Kolappa K, Dua T. The need for a better global dementia response. *Lancet Neurology* 2021.
93. Ang TFA, An N, Ding H, et al. Using data science to diagnose and characterize heterogeneity of Alzheimer's disease. *Alzheimer's Dement* 2019; 27: 264-271.
94. Seshadri S, Beiser A, Au R, et al, Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 2. *Alzheimer's Dement.* 2011; 7(1): 35-52.
95. Akinyemi RO, Yaria J, Ojagbemi A, et al. Dementia in Africa: Current evidence, knowledge gaps, and future directions. *Alzheimer's Dement.* 2021.