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Circulating Biomarkers for Alzheimer's Disease: Unlocking the Diagnostic Potential in Low- and Middle-Income Countries, Focusing on Africa

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Abstract
Background: Alzheimer's disease (AD) is emerging as a significant public health challenge in Africa, with predictions indicating a tripling in incidence by 2050. The diagnosis of AD on the African continent is notably difficult, leading to late detection that severely limits treatment options and significantly impacts the quality of life for patients and their families. ***Summary:*** This review focuses on the potential of high-sensitivity specific blood biomarkers as promising tools for improving AD diagnosis and management globally, particularly in Africa. These advances are particularly pertinent in the continent, where access to medical and technical resources is often limited. ***Key Messages:*** Identifying precise, sensitive, and specific blood biomarkers could contribute to the biological characterization and management of AD in Africa. Such advances promise to improve patient care and pave the way for new regional opportunities in pharmaceutical research and drug trials on the continent for AD.

Introduction

Alzheimer's disease (AD) is a chronic and debilitating condition characterized by progressive decline in cognitive functions [1]. The impact of AD is significant, affecting approximately 50 million people globally, with over 2 million cases reported for dementia in Africa [2]. The prevalence of AD on the African continent is particularly alarming, rising from 3.6 million cases in 2020 to an estimated 16.2 million by 2050 [3] (Fig. 1). This increasing

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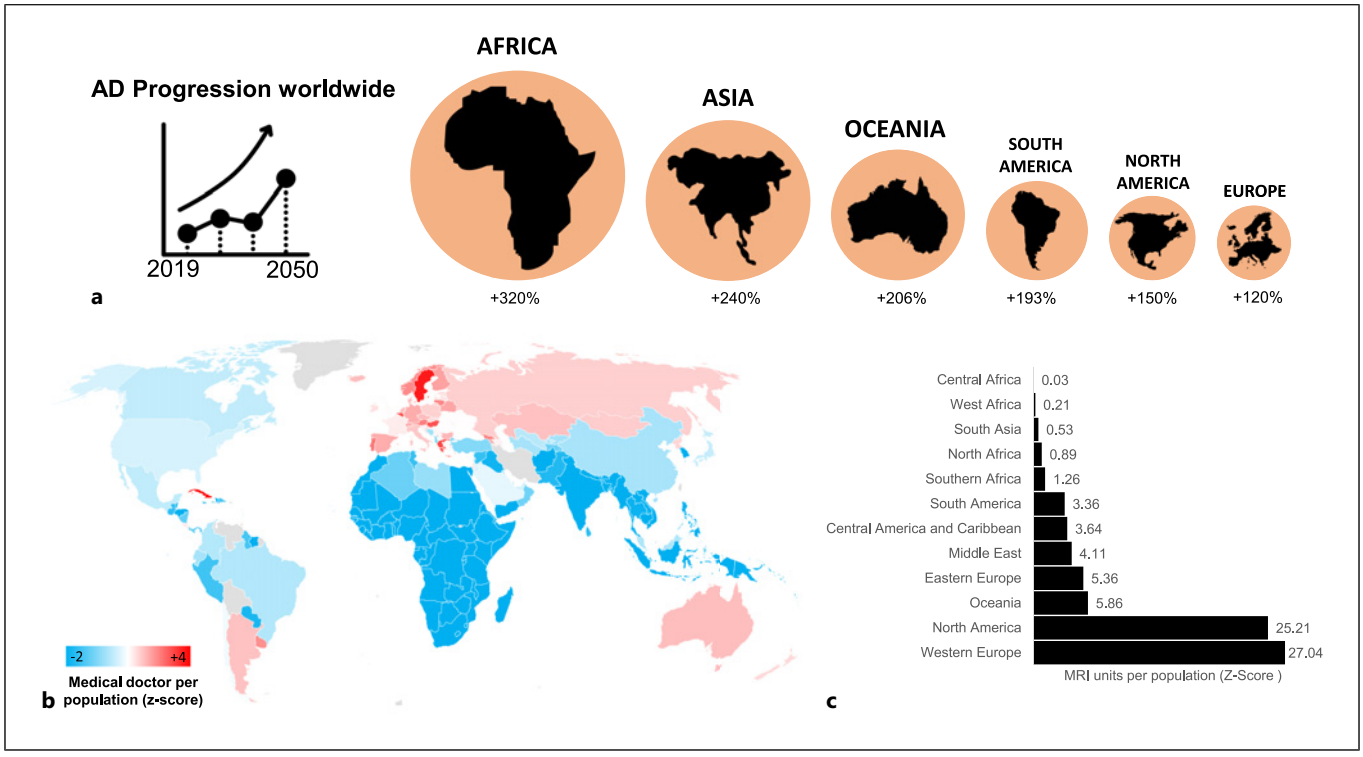

Fig. 1. Alarming surge in AD cases expected in Africa by 2050. **a** Diagram illustrating the projected increase in AD across the continents. **b** Map displaying doctor-to-population z-scores by country. **c** Histogram showing the average MRI densities (z-score) by continent in 2019. The data for this figure were obtained from the WHO website (https://www.who.int).

trend, exacerbated by demographic and epidemiologic transitions coupled with increased life expectancy, is poised to lead to substantial socioeconomic consequences for patients and families and large pressure on healthcare systems in Africa [2]. Significant advancements have been made since 2011 in the understanding of the pathophysiological mechanisms of AD [4]. These insights have led to considerable progress in diagnostic and treatment approaches. The use of biomarkers, such as tau and amyloid-beta, has been instrumental in shifting the focus toward in vivo detection of AD [5]. Despite these advances in vivo AD diagnosis mainly found in high-incoming countries and recent advancements in the development of anti-amyloid drugs that aim to reduce AD morbidity [6]. Africa is far from these current advancements and faces unique and pressing challenges in the diagnosis and management of AD (Table 1) [3]. The African continent faces a shortage of neuroimaging techniques, such as magnetic resonance imaging (MRI) and CT scans, high cost of these equipment, their maintenance, and lack of sufficient trained personnel [7, 8]. In addition to these challenges, socioeconomic and cultural barriers limit the application of certain diagnostic procedures such as lumbar puncture [2, 9]. Therefore, there is a critical need to explore new context-appropriate approaches to enhance AD diagnosis and management in Africa, and one of the most promising approaches could be measuring circulating proteins, such as tau, amyloid-beta, neurofilament (NfL), and glial fibrillary acidic protein (GFAP), which are associated with Alzheimer's and related dementia [10]. These proteins, detectable in biofluids such as cerebrospinal fluid (CSF) and blood, could offer a more accessible method for garnering valuable biological insights into AD [10, 11]. The implementation of circulating biomarkers could potentialize the current diagnostic process, guide the selection of additional diagnostic tools, and significantly influence patient treatment strategies by contributing to the identification of suitable candidates for anti-amyloid drugs and inform the management of other neurodegenerative diseases. The current lack of biological characterization of AD in low- and middle-income countries

Table 1. Summary of the different challenges related to diagnosis access for AD in Africa

Not enough healthcare resources
Concerns about certain diagnostic methods
Not enough specialized doctors or centers
Inadequate healthcare coverage
Expensive diagnostic tools
Unsuitable nature of tools to local culture and education levels
High economic burden, along with other health priorities
Lack of data on dementia and CSF biomarkers

(LMICs), particularly Africa, highlights the urgent need to include these regions in ongoing clinical trials [12]. Utilizing circulating biomarkers can provide a more readily available approach for defining the biological aspects of AD in Africa. This review aimed to explore current diagnostic models for AD, discuss selected combined profiles of circulating biomarkers and their potential benefits, and discuss the prerequisites for their implementation in Africa.

Current Diagnostic Models of AD and Application Challenges in LMICs

A Perspective from High-Income Countries

The initial clinical criteria for AD have been established since 1984, focusing primarily on clinical symptoms [13]. In 2011, a significant revision was made by the National Institute of Aging (NIA) and Alzheimer's Association (AA), which included definitions of preclinical and mild cognitive impairment (MCI) stages of AD and related disorders [4]. This revision also integrated the biological definition of AD with the inclusion of tau and amyloid CSF biomarkers [14]. These advancements have significantly improved the diagnosis of AD, transitioning from postmortem diagnosis to in vivo detection using a combination of clinical and biological markers [15]. The National Institute of Aging (NIA) and Alzheimer's Association (AA) proposed the concept of categorizing the clinical phenotypes of individuals with AD by utilizing biomarker evidence in the CSF and neurodegeneration [16]. This system evaluates the presence of β-amyloid (A), hyperphosphorylated tau (T), and neurodegeneration (N), resulting in 8 possible combinations of biomarkers based on clinical profiles [16]. This classification is based on a comprehensive clinical diagnostic approach that includes neurological and/or psychiatric assessment. Neuroimaging techniques, such as MRI and positron emission tomography (PET), are employed as exploratory tests to support diagnosis by ruling out other conditions or confirming specific clinical features [17]. Alzheimer's diagnosis is confirmed by measuring biomarkers present in the CSF, such as the Aβ42/40 ratio, Aβ1–42, p-tau, and total tau [16]. These biomarkers help reduce the diagnostic error rate, which can be as high as 40–45%, when relying solely on clinical-radiological reasoning in cases of degenerative amnesic syndrome, as reported by Landau et al. [18]. However, depending on the availability of appropriate health systems and medical resources, the accessibility of this diagnostic procedure is limited in resource-constrained countries, such as those in Africa. The current diagnostic guidelines for AD without blood biomarkers in clinical settings also warrant reconsideration of the existing NIA-AA criteria, which will hopefully be updated [16].

Evolution of AD Pathology and Diagnosis: A Historical and Contemporary Perspective in Africa

In the context of diagnosing AD in Africa, advancements in biological characterization have presented a limited number of studies focused on Africa's native population, with the majority related to epidemiological investigations [2]. Since 1984, studies such as those by Ogeng'o et al. [19] paved the way for presenting the first postmortem characterization of cerebral amyloid β protein deposits and other Alzheimer's lesions in elderly cohorts from Nairobi and Dar es Salaam. In 2015, Seggane Musisi and Stanley Jacobson's book depicted the radiologic presentation of brain degeneration and dementia in sub-Saharan Africa [20]. While studies on circulating biomarkers mainly rely on black American data, Chaudhry and Rizig [21] meta-analysis highlighted the lack of diverse inclusion, noting disparities in CSF t-tau and p-tau181 levels between African Americans and white Americans, with no studies on native Africans finding. Other significant studies by Gureje et al. [22], Hendrie et al. [23], and Naslavsky et al. [24] showed varying impacts of APOE ε4 on AD depending on ancestry. Kim et al. [25] identified the risk gene CD2AP in association with plasma homocysteine levels in the African American and Yoruba cohorts. Despite ongoing research by the African Dementia Consortium [26], there are still significant gaps in robust biological AD characterization in Africa, which could be due to a variety of factors, including limited regional and international research funding and challenges in the availability and cost of diagnostic tools. Neuroimaging tools, such as MRI and CT scans, are prohibitively expensive in sub-Saharan Africa, making significant obstacles regarding diagnosis

accessibility given the average income in Africa [27]. The lack of universal health coverage in many countries is one of the several factors affecting AD management in Africa [28]. The high costs associated with neuroimaging tools add to the cost of specialized physician consultation, which leads some patients to seek alternative solutions, including traditional medicine or religious practices [2, 29, 30]. Practitioners in resource-limited settings often resort to less expensive diagnostic modalities based on clinical evaluations and the use of less specific techniques, such as CT scans or EEGs [31]. Although these methods are more accessible, they are not reliable for identifying AD. The challenges in the longitudinal monitoring and evaluation of patients, particularly in the use of CSF, are compounded by ethical considerations regarding techniques such as lumbar puncture, particularly in older patients [9]. In Africa, where life expectancy ranges between 58 and 65 years and treatments are not widely available, families often question the necessity of invasive procedures [9, 32]. Cultural beliefs also influence the perceptions of neurocognitive impairment, often seen as a normal part of aging [2, 29]. Additionally, the limited availability of multidisciplinary centers and a shortage of trained healthcare professionals significantly impede an effective response to AD in some countries, such as Cameroon in Africa, which has only approximately 60 psychiatrists and 35 neurologists for a population of over 25 million [33]. Nevertheless, the clinical neuroscience training programs in the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I are increasing their output of brain health professionals, which could bridge these gaps in care and expertise [33]. There are still African countries that lack adequate neurologists [34]. This shortage of trained healthcare professionals and absence of centers of excellence present significant challenges for community-based AD diagnosis and care. However, these challenges are poised for improvement through initiatives such as task-shifting and outreach programs [35]. These initiatives are expected to be significantly bolstered by the collective efforts of scientists across the continent under the auspices of the Africa Dementia Consortium (ADC) [26]. By combining dementia researchers in a multidisciplinary framework, ADC aims to generate comprehensive clinical and socioeconomic datasets that are crucial for improving the characterization of dementia phenotypes in Africans. These include epidemiological studies focusing on the prevalence, incidence, and risk factors of dementia, genetic and epigenetic research to understand hereditary influences, and identification of unique biomarkers for more precise diagnosis. For future research endeavors, ADC intends to leverage existing resources such as the biobanks of brain samples, CSF, and blood [36]. This comprehensive approach of ADC is set to fill critical gaps in dementia research and care in Africa, offering hope for improving management and understanding of AD in Africa [26]. In the era of intensive research on anti-amyloid drugs that could potentially reduce AD-related morbidity in the coming years, those without biological characterization, such as the native African population, are excluded from current clinical trials [12]. Circulating biomarkers could reduce the diagnostic error rate by as much as 40–45%, as noted by Landau et al. [18] in 2016, which relies mainly on clinical-radiological evidence in Africa and could serve as effective preliminary screening tools for AD diagnosis by identifying individuals who are more likely to benefit from further, more expensive, and less accessible diagnostic methods, such as CT scans or MRI, and could open regional anti-amyloid clinical trials by detecting amyloid-positive individuals, making suitable candidates for emerging anti-amyloid drugs. This targeted approach could not only optimize the use of context-appropriate diagnostic tools but also ensure that patients receive care tailored to their specific conditions, contributing to a more efficient, cost-effective, and culturally sensitive AD diagnosis and management in Africa.

Current Trends of Research on Circulating Biomarkers for AD

Circulating biomarkers found in biofluids such as blood provide valuable information regarding the diagnosis and progression of AD [10]. Biomarkers, such as proteins, nucleic acids, microRNAs, and extracellular vesicles (EVs), can be measured using minimally invasive blood sampling techniques (subcutaneous venipuncture), offering an alternative to current diagnostic procedures for diseases [37]. Blood sampling is a simple and accessible procedure that can be performed in various healthcare settings with very low levels of health personnel, making it suitable for resource-limited regions such as Africa. The minimally invasive nature of blood biomarkers could reduce the discomfort and lack of accessibility associated with invasive procedures such as lumbar puncture [9].The blood-brain barrier (BBB) has been shown to be affected during AD [38]. Due to the breach of the BBB, proteins and nanoparticles, including exosomes, can leak into the bloodstream. These biomolecules hold potential for the diagnosis of Alzheimer's (Fig. 2) [39, 40]. Research on blood biomarkers for AD has made significant progress, focusing on identifying

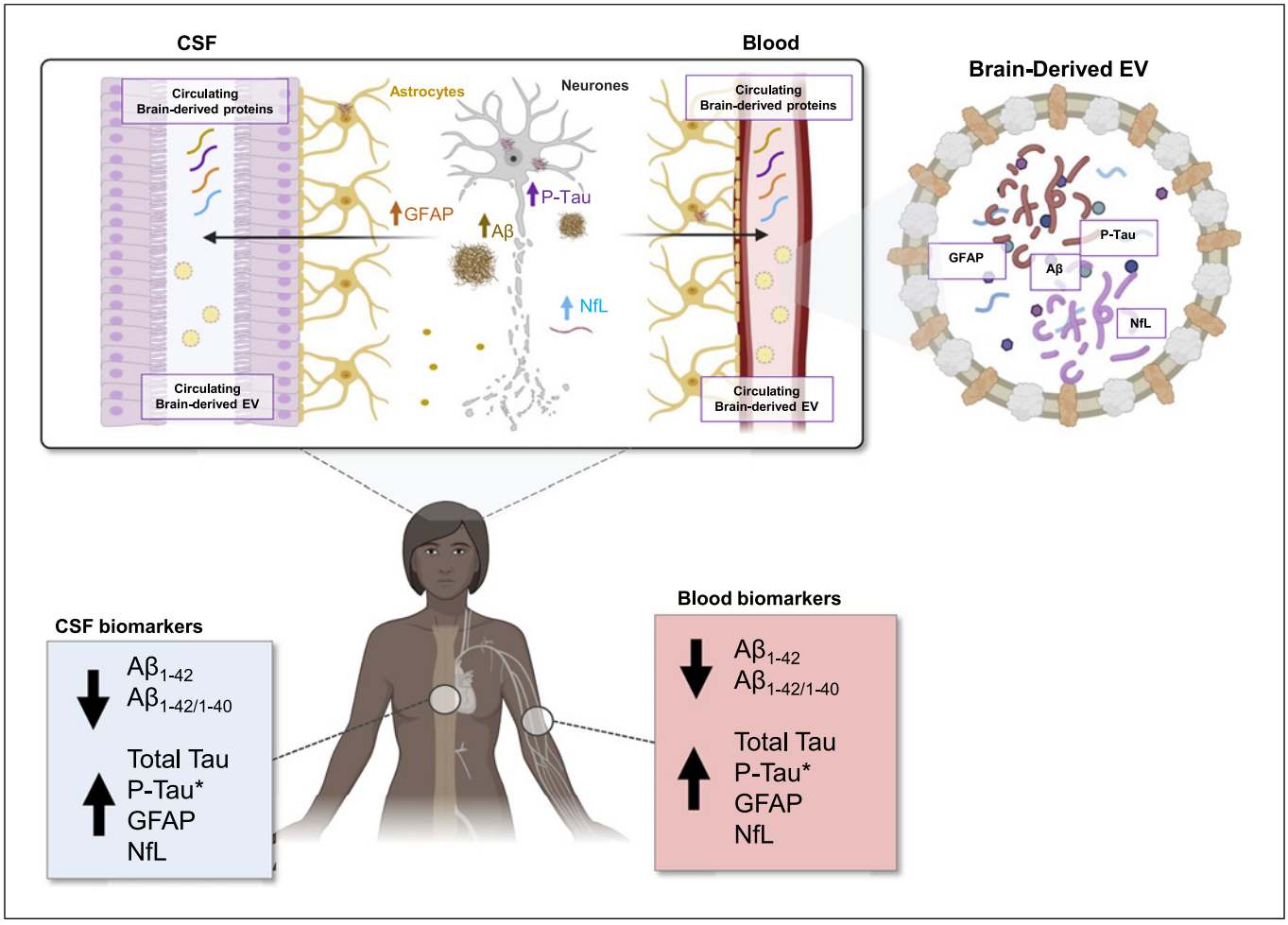

Fig. 2. Brain secretome: a promising diagnostic tool for AD. This illustration depicts the various proteins increased (arrow up) and decreased (arrow down) in the brain of an Alzheimer's patient, which are secreted into biofluids such as cerebrospinal fluid (CSF) and blood in free form (circulating brain-derived protein) or in EVs (circulating brain-derived EV).* for p-tau include p-tau181, p-tau199, p-tau202, p-tau205, p-tau217, p-tau231, and p-tau396.

reliable markers for screening processes in research settings and monitoring clinical trial [10]. The development of highly sensitive devices/systems for detecting these biomarkers in blood has also increased. Some of the most promising biomarkers studied and developed in high-income countries are as follows:

Tau Proteins

Tau is a microtubule-binding component that facilitates microtubule polymerization and stability of microtubules [41]. The human tau protein is encoded by MAPT, which is located on chromosome 17 and consists of 16 exons [42]. Alternative splicing of exons 2, 3, and 10 generates up to six tau isoform variants in the human brain [43]. In the normal adult human brain, a balanced ratio of 3R and 4R tau isoforms is maintained [44]. However, in AD and other tauopathies, imbalanced 3R: 4R tau isoform ratios in the brain can occur because of altered MAPT pre-mRNA splicing, leading to neurotoxicity [45]. These imbalances adversely affect pre- and postsynaptic compartment synaptosomes, causing a disruption in microtubule assembly, axonal transport, and pre- and postsynaptic functions, eventually leading to neuronal cell death during the later stages of AD [46]. In AD, tau protein tends to aggregate and become hyperphosphorylated, with several phosphorylated sites identified [47]. To diagnose AD, researchers often focus on threonine-181 (p-tau181) and p-tau217 as significant tau

phosphorylation sites in the CSF. An increase in phosphorylated tau 181 and 217, total Tau in the CSF, and functional neuroimaging are considered the gold standard diagnostic markers for AD [47]. Recent research in the context of AD indicates that changes in the levels of total tau and phosphorylated tau isoforms 181 and 217 can be detected in the bloodstream due to neuronal damage and neurodegeneration [48]. A probable practical approach for identifying patients with AD using tau blood tests could include setting a high cutoff for the p-tau217/total tau ratio and amyloid 42/total tau ratio in blood tests, which appears to correlate well with neurofibrillary tangles in research settings and could further enhance AD diagnosis in clinical setting [49]. Research on the relevance of tau proteins in the African context is essential to assist in the preliminary process and enhance clinical trial selection and monitoring. This is particularly important given the prevalence of other types of dementia, such as vascular dementia, which could also influence tau measurements. Understanding the specific role and regulation of tau proteins in native African populations will be crucial for developing more accurate biological definitions for AD and related dementias.

Beta-Amyloid (Aβ)

Beta-amyloid peptides are essential components of amyloid plaques found in the brains of individuals with AD [50]. Alzheimer's is characterized by amyloid β-protein (Aβ) deposition plaques within the brain parenchyma and phosphorylated tau in neurofibrillary tangles in neurons [51]. In the past, the diagnosis of Alzheimer's relied on postmortem brain tissue analysis in the presence of neurofibrillary tangles. Recent advancements in imaging technologies, such as PET for brain Aβ deposition and CSF Aβ biomarkers, have significantly improved diagnosis [52, 53]. In exploring AD biomarkers in biological fluids, particular focus is given to Aβ and tau proteins, which play central roles in AD pathogenesis [54]. Aβ in brain plaques consists of 40–43 amino acids, with Aβ42 and Aβ40 being the primary species generated through proteolysis of amyloid precursor protein (APP) by β- and γ-secretases [55]. Most APP undergoes non-amyloidogenic processing by α-secretase, which results in the formation of a non-amyloidogenic fragment called p3. Aβ42 and Aβ43, the longer species, have a high tendency to aggregate and deposit early in the brain, leading to the formation of highly toxic oligomers that harm neurons [56]. In contrast, Aβ40 may have antioxidant and anti-amyloidogenic effects [57]. Dysregulation of amyloid deposition significantly affects glial cells, thereby facilitating detection of Aβ pathology in the brain through plasma Aβ peptides [58]. The biomarker signature of Alzheimer's pathology is characterized by a relative decrease in the Aβ42/40 ratio [59]. This decrease is likely due to the sequestration of Aβ42 in the brain tissue, leading to a lower plasma Abeta42/40 ratio, indicative of AD pathology in the brain [59]. Recent studies have identified measurable plasma Aβ42 levels in AD patients, highlighting their potential as diagnostic biomarkers [60]. However, the specificity and sensitivity of plasma Aβ42 are somewhat limited, leading to possible false positives in non-AD patients and false negatives in those with Alzheimer's [61]. Ongoing efforts are focused on enhancing the accuracy of plasma Aβ42 as a diagnostic tool [62]. This is crucial to avoid potential overdiagnosis associated with amyloid-positive profiles in normal aging or positivity due to other amyloid pathological processes such as cerebral amyloid angiopathy [63, 64].This highlights the importance of a multidisciplinary assessment, combining plasma Aβ42 with other biomarker profiles, such as Tau proteins and other protein related to other neurodegenerative pathways such as NfL could improve diagnostic accuracy for AD and related dementia in Africa [65–67].

Neurofilament Light

Neurofilament light (NfL) is a prominent protein found in all axons of the neurons in the central nervous system [68]. It forms cylindrical and light subunits, constituting the dynamic network involved in neuronal differentiation and providing structural support to neurons [68]. Neurofilaments play essential roles in axonal growth, stability, maintenance of mitochondrial stability, and microtubule content [69]. Additionally, distinct neurofilament isoforms have been discovered to maintain the structure and function of dendritic spines associated with the synaptic status [70].

Neurofilament light is particularly crucial to study, as it seems to be involved in various pathophysiological processes leading to neurodegeneration [71]. Following axonal damage or neurodegeneration, neurofilaments or their fragments are released from the neurons [72]. The specific peptide species released and the mechanisms responsible for their release have not been clearly characterized [69]. This release can occur actively, for example, through exosomes, or passively due to loss of neuronal membrane integrity [73].

Different supramolecular structures or isoforms of neurofilaments may exhibit different degradation rates [69]. Studies on pathways for trafficking other proteins suggest that degraded neurofilament proteins may enter the peripheral circulation via perivascular drainage along

the basement membranes of arteries, eventually reaching the cervical or lumbar lymph nodes and entering the blood [69]. In the central nervous system, NfL (the most soluble and abundant subunit) is likely to be released from damaged neurons into the blood following neurodegeneration or axonal damage [74]. This makes NfL a valuable marker for neuronal damage, especially in brain diseases such as AD, multiple sclerosis, or motoneuron disease [75–77]. Recent studies have shown increased NfL levels in the CSF and blood of patients with AD, with significantly higher plasma NfL levels in patients with AD and MCI than in controls [78]. These studies have also associated NfL with cognitive, biochemical, and imaging hallmarks of the disease [79]. Consequently, researchers have proposed plasma NfL concentration as a minimally invasive biomarker for assessing neurodegeneration in AD and other brain diseases [80]. Considering the potential of NfL biomarkers in monitoring AD progression, NfL could be helpful in assessing early neurodegeneration, thus aiding decision-making for the preliminary screening process in LMICs. It is crucial to standardize the measurements of NfL biomarkers accurately while also considering potential biases, such as age, dementia staging (non-demented, MCI, dementia), and other neurological disorders, which could significantly impact its biological relevance. Moreover, the general increase in NfL may complement p-tau and Aβ biomarkers, as it captures a broad spectrum of neurodegenerative diseases in Africa. Investigating the relationship between AD-specific p-tau217 and the general neurodegeneration marker NfL in Africa could offer a promising direction for molecular epidemiological studies.

Glial Fibrillary Acidic Protein

Astrocyte activation, a principal component of the BBB, leads to the secretion of specific proteins including GFAP [81, 82]. GFAP exhibits increased expression and concentration in proximity to Aβ plaques [82]. This process contributes to the accumulation of other proteins, such as tau, which further complicates the disease [83]. More recently, Bellaver et al. [58] conducted a multisite study involving three cohorts, demonstrating that the presence of astrocyte reactivity assessed by plasma GFAP levels could represent a pivotal biomarker abnormality for biologically determining the association between Aβ burden and early tau phosphorylation and aggregation in preclinical AD and for selecting cognitively unimpaired individuals for clinical trials. This finding is particularly significant for identifying cognitively unimpaired individuals who may be potential candidates for clinical trials [58]. This detection is particularly relevant for identifying individuals at high risk of developing amyloid pathology, allowing for timely stratification and intervention [58]. Studies assessing the accuracy of plasma GFAP in the context of AD, particularly in relation to neuroinflammation induced by comorbidities such as infectious and vascular diseases, could be beneficial in Africa.

Combining Validation of Current Circulating Biomarker Profiles Could Offer Potential Biological Evidence of AD in Native African Patients

The field of AD diagnosis through circulating biomarkers is incredibly dynamic, and ongoing research aimed to enhance their accessibility in resource-constraint countries. For Africa which present different comorbidity such as infectious diseases, cardiovascular and metabolic disorders, it could be challenging to define AD limited to A+ T+ profiles pushing us to believe that validation of the combined profiles of biomarkers panels in multidisciplinary approach combining clinical phenotype with biomarkers panel where NfL (indicative of neuronal damage and aspecific neurodegeneration), beta-amyloid ratio (reflecting altered amyloid homeostasis), various forms of p-tau (signaling disruption of tau homeostasis), genotyping characterization (African polygenetics risk and epigenetics factor) [84], and GFAP (indicative of altered astrocytic homeostasis) in the context of AD could be a potential strategy to navigate into biological definition of AD in Africa context strategy [16, 58, 65–67, 85].

For individuals with cognitive impairment or MCI who are plasma biomarker profiles categorized as either Aβ-positive/tau-negative (A+/T−) or Aβ-positive/tau-positive (A+/T+), knowing that amyloid presence could be detected in the normal aging state or indicate a preclinical Alzheimer's pathological change without AD symptoms, plasma GFAP levels could indicate Aβ burden and early tau phosphorylation and aggregation, contributing to the assessment of the risk of developing AD or other types of dementias and for patients presenting clinically with an AD-like phenotype and plasma AD biomarker profiles (A+; T+) [16, 58, 65–67, 85], neurofilament light chain (NfL) can be used to evaluate additional neurodegenerative pathways [80]. These efforts aim to mitigate the risk of false-positive biomarker profiles and also highlight the necessity for a comprehensive evaluation of AD diagnosis by integrating Africa biological data in global AD scope and could be particularly valuable in the selection and expansion of candidate pools for regional clinical trials regarding the hope around anti-amyloid drugs or other current AD drug trial [6, 86].

Extracellular Vesicles

One of the major challenges associated with highly expressed brain-derived proteins is their low detection in the blood [87]. This is primarily due to the masking effect of overexpressed proteins, such as albumin and immunoglobulins, which can sometimes bias the results [88]. Additionally, the presence of proteases in the blood may contribute to the degradation of key diagnostic proteins [89]. In this context, researchers have focused on circulating EVs in blood as potential carriers of biomarkers [90]. EVs are nanoparticles composed of a lipid bilayer that surrounds various bioactive cargo [90]. For example, EVs can contain lipids, proteins (and protein aggregates), DNA, RNA (including mRNA and miRNA), and functional receptors and organelles secreted by cells [91]. Unlike free proteins, this cargo is shielded from circulating enzymes by a protective lipid bilayer.

Under physiological conditions, EVs are involved in intercellular signaling, shuttling of cargo from 1 cell to another, and the intracellular degradation of debris [92]. They are secreted by all cell types, including the various brain cells. Once secreted, these brain-derived EVs (BD-EV) can remain locally in the interstitial fluid of the brain, but they can also cross the choroid plexus to enter the CSF, as well as cross the BBB to enter the peripheral vasculature [93, 94]. Therefore, we found that BD-EV circulate among free proteins in the blood.

In the context of AD, EVs are known to maintain their shuttling capacity, actively transport pathogenic tau, and seed it into recipient cells [93]. It is likely that EVs contain a wide variety of pathogenic cargo related to these disruptions, not limited to tau, which can indicate the pathological state of the brain. In this context, EVs can facilitate a comprehensive search for brain biomarkers in the blood, as the full protein content of these nanoparticles can be studied independently of contaminating blood proteins. Research combining this concept with the measurement of currently established biomarkers could yield powerful diagnostic tools, enabling clearer differentiation between healthy and AD trajectory patients in sub-Saharan Africa.

Benefits and Challenging Perspectives of Using These Circulating Biomarkers in Africa

By combining the profiles of these biomarkers, which are commonly used in research settings and drug monitoring trials, their efficiency can be valuable in the decision-making process. These biomarkers aim to provide preliminary biological insights into AD, aiding in the early identification of potential cases, which is crucial in settings where neuroimaging tools are scarce and not widely accessible. Circulating biomarkers are designed to complement traditional diagnostic methods that mostly rely on clinical-radiological evaluations in Africa. Our approach is consistent with the current diagnostic process in Africa; integrating biomarkers as part of a broader assessment strategy could provide several advantages, such as enhancing the screening process and providing an African biological definition of AD. Validating these circulating biomarkers could offer numerous advantages for the diagnosis of AD in African countries.

Accessibility and Minimally Invasive Nature of Blood Biomarkers

Blood sampling is a straightforward procedure that can be easily conducted in diverse healthcare settings in LMICs. Additionally, the majority of available quantitative or amplifying protein devices, such as mass spectrometry or SIMOA technology, are semi or not fully semi automated, opening new opportunities for research capacity building on the continent [95]. In sub-Saharan Africa, the blood is commonly used to diagnose various diseases. This minimally invasive method is more easily integrated in the diagnosis process of diseases on the continent than other techniques such as lumbar puncture [9]. Implementing blood in the screening process for AD allows for easier and broader implementation, particularly in regions with limited access to specialized facilities or resources.

Orienting the Decision-Making Process

In Africa, AD diagnosis primarily relies on clinical and radiological evidence, with a potential error rate between 40 and 45%, as reported by Landau et al. [18]. Considering Africa's unique health landscape marked by prevalent infectious and noncommunicable diseases, we propose a targeted biomarker panel comprising amyloid, p-tau, total tau, GFAP, and neurofilament light. This selection was guided by the current diagnostic process in Africa, aligned with the current NIA-AA Research Framework AT(N) classification. As already described, plasma GFAP could be particularly valuable in determining the association between the Aβ burden and early tau phosphorylation and aggregation in preclinical AD. Moreover, in patients with strong biological evidence of AD (plasma A + T+), neurofilament light can help assess axonal integrity and neurodegeneration beyond AD. In undetermined cases, additional CT scans or MRI can be instrumental in ruling out other neurodegenerative pathways in Africa, reducing the financial burden due to their primary intention use. Combining clinical diagnoses

with validated blood biomarkers also aids in timely intervention and improves therapeutic strategies for disease management.

Expanding the Framework of Clinical Trials

Circulating biomarkers offer potential extension of clinical trials for AD in LMICs, given that current global trends demonstrate the low representation of some subpopulations, such as native Africans [96]. Expanding clinical trials to diverse populations, including LMICs, is crucial to ensure the generalizability and applicability of ongoing treatment trials [12]. These can serve as measures for monitoring treatment responses, assessing disease progression, and identifying suitable participant candidates for clinical trials in the LMIC regions. Moreover, the potential of African medicinal plants as novel therapeutic approaches to dementia care in these countries can be better studied within the framework of improved traditional medicines for dementia and related disorders [97, 98]. The incorporation of blood biomarkers into clinical trial protocols allows for a more diverse population and comprehensive evaluation of therapeutic interventions, facilitating the monitoring and development of effective treatments. Therefore, circulating biomarkers may offer novel regional perspectives for clinical trials. This will enhance the inclusion of underrepresented populations and contribute to the advancement of clinical research, particularly in Africa.

Increasing Representation of Neglected Populations of African Ancestry in Global Genetic Research

Although populations from the African continent have been increasingly included in recent genetic studies, there is still a notable underrepresentation in studies focusing on circulating biomarkers for AD and related dementias. Pioneering initiatives, such as the Human Heredity and Health in Africa (H3Africa), Health and Aging in Africa (HAALSI), and Africa Dementia Consortium (ADC), are crucial in propelling genetic studies on the continent [36]. Assessing the polygenic risk of AD in biofluids could greatly enhance our understanding of the disease and ensure that genetic studies worldwide accurately represent African-ancestry populations. This focus is vital in AD research, enabling a more thorough exploration of the disease spectrum while considering the unique genetic diversity and environmental factors prevalent in African populations.

Addressing Ethical and Cultural Concerns

Practitioners often face ethical dilemmas when dealing with aging patients exhibiting neurocognitive decline, particularly in families that view it as a normal part of aging or through the lens of traditional beliefs [2]. Additionally, there is reluctance to label a condition without available treatments or because of the cost of investigation. However, with emerging anti-amyloid drugs, the necessity for screening may be more easily communicated to the patients. Moreover, the lack of strong biological evidence, which can be addressed using blood biomarkers, may help resolve these ethical and cultural concerns.

Table 2. Summary of the benefits of using circulating biomarkers for AD in Africa

Providing biological support for the screening process
Expanding clinical trials with diverse participants
Inclusion of populations of African ancestry in genetic studies
Dealing with ethical and cultural issues
Establishing patient cohorts for disease monitoring over time
Speeding up diagnosis confirmation talks
Improving patient counseling and support
Demystifying disease misconceptions using evidence
Using easy and appropriate technology for biomarker measurement
Cost-effective and minimally invasive approaches
Increasing global biomarker data
Supporting evidence-informed policy

Requirements before Implementing Circulating Biomarkers in LMICs

Although the potential benefits (Table 2) of using circulating biomarkers for AD in Africa and other LMICs could be promising, there are several considerations that require further investigation before their clinical application can be piloted and scaled up.

Infrastructure

Infrastructure plays a major role in the successful use of circulating biomarkers for AD diagnosis and research. This requires the availability of equipment, such as proteomic and quantitative amplifying protein detection devices, which are expensive and require the presence of trained bioengineers and other specialized researchers in the region. In addition, the availability of computational devices for analysis and a reliable electricity supply is essential for sample preservation, processing, and analysis. However, overcoming the challenges related to protein/EV extraction, proper sample handling, training national teams, and establishing a robust supply system

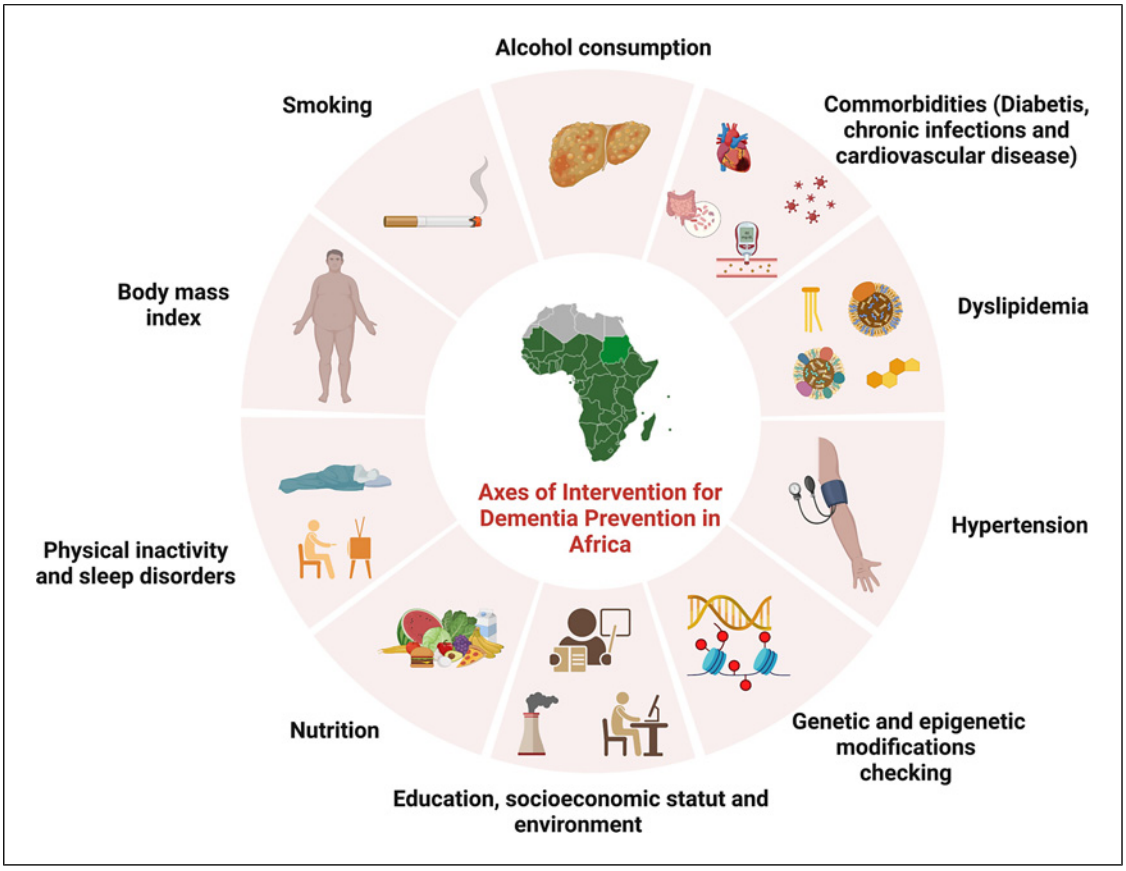

Fig. 3. Summary of possible areas of intervention for dementia prevention in Africa. This illustration describes the areas of intervention essential for preserving cognitive health in Africa's diverse landscapes. From community education to targeted healthcare, these strategies address the unique challenges faced by the continent in its fight against dementia.

on the continent is possible in the short term, whereas other aspects can be overcome in the middle and long terms.

Stakeholders

Implementing new initiatives in resource-constrained regions, such as improving the diagnosis of ADs using circulating biomarkers, could face challenges due to specific regional legislation and regulations. Administrative procedures for ethics in research or clinical applications of research could be long and difficult to obtain, especially when other prevalent diseases with higher epidemiological burdens are prioritized in these countries. Convincing regional healthcare authorities or researchers to adopt new initiatives or deviate from their usual processes may be challenging. Therefore, it is crucial to include all stakeholders, especially key stakeholders, in the discussion and fully involve them in every project, collaborating with national teams and initiatives to increase their sensitivity, participation, and ownership of change. This approach is vital to advocate for action, policy development, and support in the region regarding the importance and urgency of the diagnosis and management of AD and related dementias, as was recently declared in Nairobi during the LMIC conference on dementia [36]. Examples of networks and partnerships established by the Africa Dementia Consortium, Africa Biofluid Brain Biobank (A4B), and the Brain Research Africa Initiative (BRAIN) can be very useful in this regard [99].

Standardization of measurement techniques, including sample collection, processing, and analysis methods, is crucial for ensuring consistent and comparable results across different studies and settings. Collaborative efforts among researchers, training of national healthcare professionals, and the creation of regional and subregional centers of excellence for AD

research, diagnosis, and management can lead to the establishment of consensus guidelines for standardizing measurement techniques.

Validation

Validation studies in diverse populations are essential to assess the diagnostic accuracy and clinical utility of circulating biomarkers. These studies should consider various factors, including ethnicity, postmortem brain characterization, neuroimaging (particularly PET amyloid, or tau), CSF circulating biomarkers validation, genetic background, educational level, cultural and linguistic aspects of cognitive assessment, and comorbidities in Africa. These factors can significantly influence and add nuances to the biological interpretation of blood biomarkers during screening. The reliability and applicability of circulating biomarkers can be better understood through studies with a broad range of samples. Subregional and regional dementia initiatives such as the Africa dementia consortium and transnational projects such as the Africa Biofluid and Brain Biobank (A4B) present valuable opportunities for the validation and implementation of these biomarkers with rigorous study designs, comprehensive data analysis, and careful consideration of covariates that may impact biomarker utilization to ensure the accurate interpretation of results and diagnosis.

Feasibility Studies

Continued research efforts are required to identify novel biomarkers for the diagnosis of neurodegenerative disorders on the continent, not limited to the current candidates. Emerging technologies, such as proteomics, metabolomics, and genomics, can aid in the discovery of new biomarker candidates in different African subpopulations. By exploring these avenues, more specific and sensitive circulating biomarkers can be identified, leading to improved diagnostic accuracy and monitoring of neurodegenerative diseases in Africa and in other LMICs.

Prevention

We firmly believe that implementing risk-reduction strategies even before the onset of dementia symptoms is a valuable and cost-effective approach for integration into the dementia plan framework in the African context. This strategy entails a strong emphasis on potential interventions addressing cerebrovascular risk factors, identification of genetic risks and epigenetic modifications, effective management of comorbidities, consideration of socioeconomic factors, and promotion of education within the region [100] (Fig. 3). Additionally, promoting lifelong cognitive reserve [101], cultivating a resilient environment, promoting brain activity, and necessitating the active participation of practitioners, populations, local associations, government bodies, and all stakeholders are necessary to ensure effective communication and comprehensive strategies [101]. Interventions targeting molecular mechanisms related to aging modifications, such as AD and other related diseases, may be crucial for alleviating the escalating burden of dementia in Africa and other LMICs.

Conclusion

AD poses significant challenges in LMICs, especially in Africa, where the current diagnostic model relies heavily on clinicoradiological evidence. This approach leads to a high risk of misdiagnosis and excludes many patients from current clinical trials owing to the lack of well-characterized patients or a strong biological definition of AD, which is often hampered by infrastructure limitations, economic burdens, and ethical or cultural discussions. By enhancing the screening process and research in Africa, blood biomarkers could address these challenges. Combining the profiles of biomarkers associated with neuroinflammation and vascular modulation, such as GFAP, tau, Nfl, and amyloid-beta proteins, could provide a minimally invasive, cost-effective, and timely approach for decision-making. This method could also filter out patients needing additional investigations, such as CSF or neuroimaging, thereby expanding clinical trial participation in the African population. However, to fully harness the potential of circulating biomarkers in Africa, it is crucial to standardize measurement techniques and conduct validation studies that consider various confounding factors. Ongoing research efforts are essential for identifying novel biomarkers and utilizing emerging technologies for better diagnosis and monitoring of AD in the African context. This shift in the diagnostic model toward circulating biomarkers could lead to more accessible, cost-effective, and culturally appropriate healthcare in Africa. Funding and collaborative research are vital for validating and integrating these biomarkers into clinical practice, improving patient outcomes, and reducing burden on families and communities.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.R., L.N.B., and A.K.N. drafted the manuscript. K.R. designed the manuscript, and L.N.B. drafted the original draft. L.N.B. and K.R. contributed equally to this study and analyzed the data. J.E., G.A., and O.R. contributed to improvements in the diagnosis. Y.W.N., A.Z.Z., and A.K.N. improved LMIC sections. K.R., G.A., and A.K.N. were responsible for the decision to submit the manuscript for publication. All authors reviewed and edited the manuscript and approved its final version.

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