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PERSPECTIVE

Identifying sex- and gender-specific endocrinological, lifestyle, psychosocial, and socio-cultural targets for Alzheimer's disease prevention in Africans: The Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project

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Abstract

Dementia rates are rising globally, with the burden increasing most rapidly in low- to middle-income countries. Despite this, research into Alzheimer's disease and related dementias (ADRD) among African populations remains limited, with existing models based on Western cohorts that overlook sex-, gender-, and ancestry-specific factors. The Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project, hosted at the Brain and Mind Institute, Aga Khan University, Kenya, will establish a deeply phenotyped cohort of 250 African individuals across the ADRD spectrum. It will assess sex-specific risk factors linked to ethnicity, lifestyle, and endocrinological variables using fluid-based biomarkers (blood and saliva), neuroimaging (magnetic resonance imaging and positron emission tomography), and culturally adapted cognitive tests. By comparing data with Western and diasporic cohorts, the study aims to identify ancestry-specific and shared mechanisms driving ADRD risk and progression. The findings will support targeted, culturally relevant prevention and intervention strategies, addressing the underrepresentation of African populations in global dementia research.

KEYWORDS
African populations, ancestry-specific risk, biomarkers, cardiometabolic risk, culturally adapted assessments, dementia prevention, gender disparities, low-to-middle-income countries, neuroimaging, reproductive health, retinal imaging, sex differences

Highlights

- By 2030, > 78 million individuals are expected to have dementia, with the highest burden among women in low- to middle-income countries. Despite this, African populations remain underrepresented in Alzheimer's disease and related dementias (ADRD) research.
- Existing ADRD risk models fail to account for the unique influence of sex, gender, and ancestry on dementia risk. Female-specific reproductive and hormonal factors, including menopause transition and hormone therapy use, are poorly integrated into current models.
- The Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project is the first large-scale study to examine sex- or gender-specific and endocrine contributors to ADRD in an African population, using advanced diagnostic, biomarker, and culturally adapted cognitive assessments.
- The study will assess how biological (hormonal, metabolic), lifestyle (physical activity, diet), and socio-cultural (education, health-care access) factors interact to influence ADRD risk in African women.
- Insights from FemBER-Africa will inform the development of sex- and gender-specific, culturally adapted ADRD prevention strategies, enhancing the precision and equity of dementia mitigation efforts globally.

1 | BACKGROUND

By 2030, dementia will affect ≈ 78 million people, most of them women living in low- to middle-income countries (LMICs).[1] Early identification and management of modifiable risk factors are key strategies for mitigating this growing public health challenge.[2] However, only 0.1% of global brain health research originates from Africa—the lowest volume among LMIC regions.[1] Despite increasing evidence supporting the value of early-stage risk reduction strategies, there remains a significant gap in understanding sex-specific and ancestry-specific dementia risk profiles, particularly in African populations.

Existing models for Alzheimer's disease and related dementias (ADRD), largely derived from Western cohorts, under-represent African populations despite distinct genetic, vascular, and metabolic profiles. African studies to date have focused mainly on genetics with limited integration of lifestyle, sex, gender, and socio-cultural factors,[3,4] leaving mechanisms of risk and resilience poorly understood.

1.1 | Sex-specific biological risk factors for ADRD in African populations

Female sex is a well-established risk factor for ADRD, with women exhibiting higher age-adjusted prevalence rates and steeper cognitive decline compared to men.[5] African-based population studies report a similar trend, with more women being at risk of dementia.[6] Genetic factors may further contribute to this sex-based disparity, with evidence suggesting that apolipoprotein E (*APOE*) ε4 shows a stronger association with tau pathology in women of African ancestry, whereas *APOE* ε2 appears protective in European women and African men.[7,8]

Broader health profiles also shape sex-specific dementia risk. In sub-Saharan Africa, non-communicable disease (NCD)-related deaths and disability-adjusted life years are higher among men than women for most conditions, especially cardiovascular diseases and respiratory diseases. However, the burden of mental health disorders is higher among women. Reproductive health issues and maternal conditions also contribute significantly to the NCD burden for women.[9] These differences suggest that African men and women may have distinct pathways to dementia, shaped by their broader health profiles.

In Western cohorts enriched with diasporic participants, cardiometabolic factors mediate much of the racial/ethnic ADRD risk, yet age-adjusted risk remains highest in women of African ancestry.[3] In Nigerian residents, we observed higher incident dementia in women (hazard ratio [HR] 1.49, $P < 0.001$) alongside under-diagnosed hypertension/diabetes and more abnormal cardiometabolic markers, underscoring the need for sex-specific interventions.[10]

The complex interaction of genetic and cardiometabolic risk factors may be compounded by hormonal changes that occur with aging for both sexes. Alongside menopausal transition experiences (age at onset, symptomatology), emerging evidence indicates that reproductive and hormonal factors, including fertility history, parity, use and type of menopause hormone treatment (MHT), are critical modifiers of ADRD risk in women.[5,11] The menopausal transition constitutes a cascade of changes in neuroendocrine markers, alongside significant vascular, metabolic, immune, and neurophysiological changes, which may heighten ADRD risk.[12] Menopausal timing and symptom profiles have been shown to vary by race and ethnicity.[13] Furthermore, females of African ancestry report greater symptom severity compared to those of other ancestries,[14] potentially influencing dementia risk trajectories from mid to late life.[15] Among males, studies have found lower testosterone concentrations are associated with increased ADRD risk.[16] However, this evidence is largely derived from Western populations, and there is currently a lack of data on whether similar associations exist among males of African origin.

1.2 | Gender-specific determinants of ADRD in African populations

In addition to biological factors, socio-cultural and lifestyle determinants play a pivotal role in shaping ADRD risk in African populations. Both Duodu et al.[6] and our pilot data suggest socio-cultural stressors, such as malnutrition and multidimensional poverty, further compound the biological risks for African women relative to men, propounding the need for gender-informed mitigation strategies that are culturally relevant. Socio-economic inequities in education and occupational attainment, along with gendered disparities in access to health care and social support, as well as gender-based violence and norms regarding societal roles[17] are possible targets for intervention. In the United States, Black women face barriers in ADRD care, leading to delayed diagnosis and treatment.[18] Exposure to structural sexism is associated with memory decline among US women, with a stronger association observed in Black women compared to White women, particularly in relation to lower baseline memory.[19] Interestingly, social determinants of health, but not genetic ancestry, predict dementia prevalence in Latin America,[20] highlighting the predominant role social determinants play in ADRD development in this region and the need for public health policies that address social disparities to effectively reduce dementia risk in these communities. To our knowledge, no systematic comparisons of social, environmental, and genetic ancestry factors have been conducted in African populations, particularly with regard to both sex and gender differences.

1.3 | Challenges and opportunities for sex- and gender-informed ADRD research in Africa

The limited availability of neuroimaging and fluid biomarker analysis infrastructure in Africa presents significant challenges for large-scale biomarker validation and longitudinal ADRD tracking. Additionally, culturally adapted cognitive assessments are still sparse, with limited normative data from African cohorts. Sex-specific factors are rarely integrated into ADRD models in general, let alone African, populations. A key challenge lies in the lack of culturally sensitive approaches for

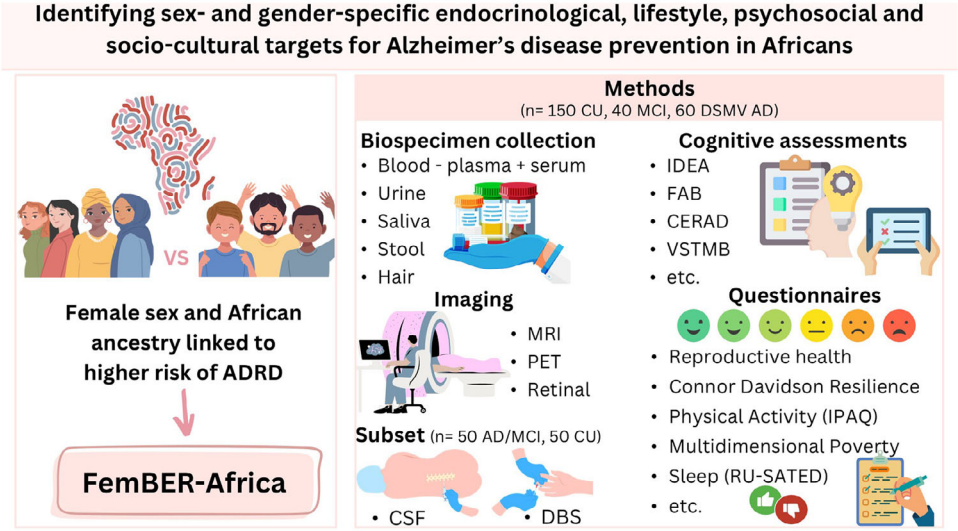

FIGURE 1 The Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project. ADD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CSF, cerebrospinal fluid; CU, cognitively unimpaired; DBS, dry blood spot; DSMV, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; FAB, Frontal Assessment Battery; IDEA, Identification and Intervention for Dementia in Elderly Africans; IPAQ, International Physical Activity Questionnaire; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; RU-SATED, Satisfaction, Alertness, Timing, Efficiency, and Duration; VSTMB, Visual Short-Term Memory Binding Test.

collecting detailed health histories around sex-specific factors, such as reproductive and hormonal histories. Questions around fertility, menopause, and hormone use can be deeply personal and culturally sensitive, making it difficult to gather accurate data. Socio-cultural determinants such as educational disparities, health-care access, and psychosocial stressors may also need to be revised from "the Western standard" to fully elucidate culturally specific risks, which may themselves be mediated by gender-specific factors.

Nonetheless, new technologies offer promising solutions. The growing momentum in African ADRD research[4] presents an opportunity to build local research capacity through collaborations with African researchers and communities. The advent of non-invasive biomarker capture techniques, such as plasma, saliva, and retinal imaging, alongside culturally adapted digital cognitive assessments, could enable cost-effective, scalable ADRD diagnosis and monitoring. Validating these methods against gold-standard diagnostic tools is a crucial next step toward establishing sustainable and contextually relevant ADRD research infrastructure in Africa.

1.4 | Sex and gender precision for ADRD prevention: the Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project

The Female Brain Health and Endocrine Research in Africa (FemBER-Africa) project (Figure 1) will establish a deeply phenotyped cohort across the ADRD continuum, integrating fluid biomarkers, neuroimaging, and culturally adapted cognitive/psychosocial assessments. The study focuses on sex-, gender-, and socio-cultural modifiers and is harmonized with Western cohorts to identify shared and ancestry-specific mechanisms. Kenya will serve as the foundational site, with phased expansion to additional sub-Saharan African (SSA) countries to enhance regional diversity and scientific capacity.

2 | METHODOLOGICAL APPROACH

2.1 | Study design

The study follows a non-interventional, cross-sectional approach. Participants will undergo initial clinical evaluation by neurologists, based at Aga Khan University Kenya Hospital (AKUH) or Kenyatta Hospital, to assess for the presence of mild neurocognitive disorder (also known as mild cognitive impairment [MCI]) or major neurocognitive disorder due to Alzheimer's disease, based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition or International Classification of Diseases (ICD)-11 criteria and all available clinico-diagnostic information. Subsequently, a one-time evaluation will include interviews, questionnaires, culturally adapted cognitive/functional assessments, and blood/saliva biomarkers. The study will encompass three participant groups: n = 250: 150 cognitively unimpaired (CU), 60 major neurocognitive disorder due to Alzheimer's disease (AD), and 40 MCI (diagnostic groups age and sex matched to 100 participants in the CU group). Mixed dementias will be classified through expert consensus, particularly in cases in which multiple etiologies (e.g., Alzheimer's disease with cerebrovascular contributions or Lewy body pathology) are suspected. Diagnostic classification will be informed by available clinical, neuroimaging, and laboratory data, including magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography (PET; where available), cognitive profiles, functional

assessment, and caregiver interview. Multidisciplinary case review panels will include neurologists, neuropsychologists, and study clinicians, who determine the most appropriate diagnostic. When ambiguity remains, participants will be assigned to a "mixed/uncertain" category and excluded from biomarker subgroup analyses to preserve interpretability.

2.2 | Study population and recruitment strategies

The study will recruit controls and cases from clinical and community settings, respectively. We plan to enroll 100 cases with MCI ($N = 40$) and AD ($N = 60$), aged ≥ 55 years, to reflect the epidemiological onset patterns of late-life cognitive impairment. These participants will be recruited from neurology clinics at AKUH and Kenyatta National Hospital. By leveraging partnerships with community-based organizations in Nairobi, we will recruit 150 CU controls, aged ≥ 35 years, to capture the impact of hormonal transitions across the female life course. Control participants will include participants socio-demographically matched to cases by age, sex, and education. Inclusion and exclusion criteria are shown in Table 1.

2.3 | Data collection

Primary data will be collected by trained interviewers (project manager, project assistants) using culturally adapted surveys, cognitive tests, and blood/saliva sampling. Secondary data will be obtained from 100 MCI/AD cases through medical records at AKUH and Kenyatta National Hospital or expert panel consensus for undiagnosed cases. Comparative analysis will include secondary data from established Western cohorts enriched with diasporic African participants.

2.3.1 | Pre-screening measure

To evaluate cognitive impairment, we will use the Identification and Intervention for Dementia in Elderly Africans (IDEA) cognitive screen. This instrument has been translated into Kiswahili, validated against clinically diagnosed dementia (area under the receiver operating characteristic curve [AUROC]: 0.87–0.89), and demonstrated minimal educational bias in various SSA contexts.[21–23] It encompasses items that gauge orientation vocabulary knowledge, visuoconstruction, and semantic fluency, along with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 10-word recall test as an indicator of verbal episodic memory.[24] Total scores range from 0 to 15. Previous validation efforts in Tanzania established the following categorizations: 0 to 7 (low performance), 7 to 9 (intermediate/borderline performance), and 10 to 15 (good performance). We aim to establish the absence of cognitive impairment in CU controls by using a cut-off score of 10 (i.e., community-ascertained controls with total IDEA score < 10 will be excluded from CU group).

TABLE 1 Eligibility criteria.

General inclusion criteria
Aged 35 years or older History of education/work experience (unlikely congenital learning disabilities)
Fluent in Swahili and/or English
Willing to give written consent and complete neuropsychological tests
Medically stable (based on self-reported history)
Willing to undergo lumbar puncture (if no contraindications)
Demonstrates capacity to consent
Healthy controls
Pre-screening IDEA score ≥ 10
Absence of cognitive decline
MCI and AD
Cognitive decline reported by participant or partner
Cognitive impairment in ≥ 1 domain (e.g., memory, language, executive function) with *z* score < −1.5
AD
Impairment in instrumental activities of daily living
Cognitive impairment in ≥ 2 domains with *z* score < −1.5
General exclusion criteria
Contraindications for neuroimaging, neuropsychology, or biospecimen assessments
History of major neurological illness (excluding dementia)
Recent significant change in neuroactive medication (> 10 mg)
- Pregnancy at the time of participation - Recent major surgery (within 8 weeks)
Inability to comply with study requirements
Specific exclusion for dementia
Advanced dementia causing undue burden and distress
Retinal imaging exclusion criteria
Advanced retinal or ocular disease
Ocular surgery within 2 months or ongoing medication
Retinitis pigmentosa

Abbreviations: AD, Alzheimer's disease; IDEA, Identification and Intervention for Dementia in Elderly Africans; MCI, mild cognitive impairment.

2.3.2 | Functional assessment/activities of daily living

We will administer 11 items from the IDEA Instrumental Activities of Daily Living scale (IDEA-IADL[25]), developed in Tanzania. These items encompass various tasks, including providing advice, resolving conflicts, passing down traditions, overseeing celebrations and ceremonies, and managing household chores, among others. The IDEA-IADL scale is available in both English and Kiswahili and has

TABLE 2 List of neuropsychological measures.

Neuropsychological domain	Neuropsychological test
Cognitive screening measure	IDEA, which includes the CERAD 10-word recall test
Adaptive functioning	IADL Making Change test Frontal Assessment Battery [S1]
Memory	TabCAT Birdwatch [S2] Brave Man Story Memory Task Paired Associate Learning Task Memory Binding Task [S3]
Language	Animal Fluency (adapted from NACC UDS, [S4]) Multilingual Naming Test (adapted from NACC UDS, [S4])
Visuospatial function, Praxis and speed	Nigerian Matchstick Test [S5] (as addition to IDEA) TabCAT Match Test [S2] The Four Mountains (4M) Test [S6]
Motor dexterity	Grooved Pegboard
Attention	Digit Span (adapted from NACC UDS, [S6]) TabCAT Flanker Test [S3]

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; IADL, Instrumental Activities of Daily Living; IDEA, Identification and Intervention for Dementia in Elderly Africans; NACC UDS, National Alzheimer's Coordinating Center Uniform Data Set; TabCAT, tablet-based Cognitive Assessment Tool.

been demonstrated to enhance discriminatory power when combined with the 6-item IDEA cognitive screen (AUROC: 0.94) for distinguishing between individuals from the community who are free from cognitive impairment and those with dementia.[21] Each item is rated on a scale from 0 (unable to perform independently) to 1 (able to perform with assistance) to 3 (able to perform without assistance). The total score on these 11 items can range from 0 to 33.

2.3.3 | Neuropsychological assessment

A harmonized neuropsychological battery, aligned with African, Western, and Latin-American studies, will yield global and domain composite scores (see Table 2; Appendix I in supporting information).

2.3.4 | Socio-demographic and social determinants of health data

We will collect or confirm age, biological sex at birth, and identified gender. To assess poverty and deprivation, we will adapt the Multidimensional Poverty Index[26] to the Kenyan context. The World Health Organization Disability Assessment Schedule II (WHO-DAS II,[27]) will be used as an additional instrument to assess social participation/engagement domain. The World Health Organization Quality of Life (WHOQOL-BREF[28]) will be used to assess quality of life. Furthermore, we will also ask supplementary questions relating to the quantity, quality, and nature of education; highest education and occupation attainment/complexity; neighborhood characteristics (rural, urban, and semi-rural areas); and current income.

Because Kenya is an ethnically and linguistically diverse country (e.g., including Kikuyu, Luhya, Luo, Kalenjin, Kamba, Kisii, Maasai, and Meru peoples as well as other minorities, such as those of Asian and European ancestry), we will co-design a sensitive questionnaire for participants' linguistic profiles (primary language, mono/bi/multilingualism, and proficiency) and ethnic and racial identities. We will collect data to characterize handedness (left, right, and ambidextrous) and marital status.

Finally, we will assess lifetime stress and resilience, using culturally adapted measures recently demonstrating construct validity in African samples. These are The Life Events Checklist,[29] which has been adapted and validated in Kenyan adults[30] and is in current use in aging studies in Kenya, and the 10-item Connor–Davidson Resilience Scale,[31] which has been translated into Swahili and culturally adapted for the current project.

2.3.5 | Clinical, health, and lifestyle factors

For CU participants, we will obtain self-reported medical history and medication use. For the subset of MCI and AD cases (n = 100), we will obtain medical history and medication use via clinical records (see section 2.4). All participants will be asked about history of traumatic brain injury (TBI) and current smoking status and history (tobacco, cannabis, shisha, and vaping); for MCI and AD cases, these will be verified against clinical records. A physical exam will record: height, weight, and body mass index (BMI); waist, hip, head, and mid-upper arm circumference; and blood pressure (measured three times while seated). We will measure nutritional status and alcohol consumption, using culture-specific questionnaires, co-developed with the stakeholder team. To assess nutritional status, participants will complete a brief dietary questionnaire adapted from established malnutrition screening tools. This includes a self-report item on unintentional weight loss over the past 3 months, with response categories distinguishing between mild and significant weight loss. In addition, BMI will be calculated from measured height and weight during the physical exam and classified into risk categories. This approach provides a rapid screening of nutritional vulnerability, which may interact with cognitive health and endocrine function, particularly in aging populations. Given the absence of a validated food frequency questionnaire for the region and the need to minimize participant burden, we do not currently assess detailed dietary intake or macronutrient composition. However, more detailed nutritional analysis may be considered in future follow-up phases. Physical activity will be captured using the International Physical Activity Questionnaire Short Form (IPAQ-SF[32]), which has been used in Nigerian adults.[33] Sleep quality will be assessed using

the Satisfaction, Alertness, Timing, Efficiency, and Duration (SATED) Questionnaire,[34] which has been translated into Swahili.

TBI is assessed using two culturally adapted questions during the medical interview. Participants are asked: "Do you have a history of significant head trauma followed by a persistent neurological deficit?" (translated into Kiswahili), to capture serious injuries with long-term consequences such as sensory, motor, or cognitive impairment. All participants are also asked: "Has there ever been a time in your life when you hit your head so hard that you blacked out?" If yes, they are prompted to report the number of such episodes. This two-tiered approach allows for the identification of both clinically significant and moderate-to-severe TBI exposures across the life course, enabling stratified analysis by severity and cumulative burden.

Known human immunodeficiency virus (HIV) status will be documented through structured medical history interviews and clinical record review, where available. Participants living with HIV will not be excluded from the study. This reflects the epidemiological reality of HIV prevalence in Kenya. Including people living with HIV enables us to examine potential differences in cognitive impairment profiles; identify patterns of accelerated or atypical aging; and explore interactions among HIV, endocrine factors, and other comorbidities. We believe this inclusive approach strengthens the study's ecological validity, facilitates comparison to prior SSA neurocognitive research, and supports the development of more representative and context-appropriate dementia risk models.

2.3.6 | Reproductive and menopausal histories

As the study is interested in sex-specific endocrinological health factors which may contribute toward or modify risk for ADRD in later life, participants will be assessed for several proxies of endocrine health and status. These include: history and age at time of reproductive surgical procedures (e.g., males: vasectomy; e.g., females: hysterectomy, ovariectomy) and hormone use (fertility treatments, acne, birth control, MHT use: current use, past use, age at time of first use, duration in months, MHT type; exogenous testosterone), puberty onset, number of children, fertility issues, and history of sexually transmitted diseases. For female participants: current menopausal status if known (pre-, peri-, and post-); menopausal transition history (if applicable); age of menarche onset and termination (if applicable); recent period history (if applicable); number of pregnancies, number of births, (include field for abortions, miscarriages, stillbirths); and age of pregnancies and births. Perimenopausal hormonal transitions may confound associations between endocrine markers and cognitive outcomes. To address this, women currently experiencing perimenopause (defined clinically as having menstrual irregularity within the past 12 months and/or follicle-stimulating hormone (FSH) levels in the transitional range) will be identified through detailed reproductive history and serum FSH assays.

2.3.7 | Collection, processing, and storage of fluid bio-samples

Trained study personnel will be responsible for the collection of various bio-samples, including blood (serum and plasma), urine, and saliva for multi-omics analysis. Cerebrospinal fluid (CSF) will be collected in a subsample ($n = 60$: 30 AD/MCI, 30 CU, age/sex matched), who will also provide dry blood spot (DBS) samples. These samples will be stored for potential future investigations related to biomarkers associated with ADRD (e.g., amyloid beta [Aβ] 42 and 40, phosphorylated tau [p-tau] 181, and synaptic markers); for collection of a DNA/RNA sample for AD-relevant genes, amyloid precursor protein/Aβ cleavage pathways, with emphasis on African-specific risk variants (e.g., *APOE* [E3:R145C]; *TREM2*; *ABCA7*, Val66Met within brain-derived neurotrophic factor) as well as to determine markers of endocrinological status (e.g., estradiol, progesterone, and testosterone levels). Hormone assays will be performed using validated immunoassays and, where possible, liquid chromatography tandem mass spectrometry platforms to ensure accuracy at low circulating concentrations typical of postmenopausal states. To improve reliability and interpretability, additional markers including FSH and luteinizing hormone (LH) will be measured to assess menopausal status and explore potential neuroendocrine contributions to ADRD. All samples for hormone analysis (blood and saliva) will be collected in the morning (between 08:00 am and 10:30 am) after overnight fasting to control for circadian rhythm effects. Saliva samples will also be collected in the evening to capture diurnal variation in cortisol and facilitate area under the curve (AUC) calculations. Adiposity measures (e.g., BMI, waist/hip ratio) and reproductive health history will be considered covariates in endocrine analyses to contextualize hormone levels, particularly estradiol derived from peripheral aromatization. Additionally, we will offer the option for participants to provide stool samples for future studies of the gut microbiome and scalp hair samples, which will be stored for potential future studies focusing on metabolic activity and endocrine markers.

To characterize the immunophenotype of individuals with MCI, AD, or who are CU, we will offer the option of collecting an additional blood sample for peripheral blood mononuclear cells (PBMCs). This will be done only if the participant consents to this supplementary assessment. The PBMCs will be used to characterize the immunophenotype associated with preclinical AD, as well as to uncover potential novel associations with AD pathology biomarkers, disease susceptibility, and clinical progression. Specifically, we will collect up to 50 mL of whole blood (within ethical guidelines for adult participants), processed for plasma, serum, and stored whole blood for immunotyping and genotyping studies.

Saliva samples will be spooled into six aliquots and will be used for analysis of AD-related biomarkers (e.g., lactoferrin, amyloid, and neurofilament light chain), cortisol, and other steroid hormones. Additionally, we will collect one urine tube, which will be stored in five aliquots, and one scalp hair sample that will be stored in foil paper.

All collected samples will be processed and bio-banked for future investigations. Blood samples, processed within 2 hours of collection and stored at −80°C, will also undergo in-country processing, including clinical laboratory investigations (e.g., HbA1C, vitamin B12, vitamin D, Thyroid Function Tests, lipid profiles, fasting blood glucose, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, and serum creatinine). The entire sample collection process is expected to take ≈ 30 minutes. These samples will be processed and securely stored in local bio-banking facilities. Select bio-samples will be shipped for specialized analysis of ADRD biomarkers in labs of expert collaborators and co-investigators.

Samples and data will be de-identified (devoid of personal identifiers) in the event of being sent to external organizations (recipient) receiving these samples. All recipients will be subject to Aga Khan University (AKU)'s Material Transfer Agreement and Data Transfer Agreement. These will outline the responsibilities of each party in the transfer of any de-identified materials and data. Recipients will agree to use the materials and data exclusively for the approved purposes without exception; the material and data will be used by the recipient in compliance with Kenyan Data Protection Act 2019,[35] General Data Protection Regulation (GDPR),[36] and Health Insurance Portability and Accountability Act (HIPAA) [37]standards; any unused material and data will either be destroyed in compliance with all applicable statutes and regulations or will be returned to AKU upon request. The handling, storage, and disposal of all biological specimens will strictly adhere to the standard operating procedures of the AKU Clinical Research Unit. Furthermore, our procedures will align with pre-analytical recommendations for subsequent analysis of AD fluid biomarkers.[38]

2.3.8 | Neuroimaging

A subset of participants ($n = 60$: 30 MCI/AD, 30 CU, age/sex matched) will undergo a neuroimaging protocol. Structural and functional brain MRI (3T Philips Ingenia scanner at AKUH, including T1-weighted sequences [repetition time (TR) = 2300 ms, field of view (FOV) = 240 x 256 x 208 mm @ 1x1x1 mm resolution, duration = 6:20 minutes) and echo-planar imaging blood-oxygenation-level-dependent (BOLD) sequences with blocks of eyes-open, eyes-closed conditions (TR = 600 ms, FA = 53° FOV = 220 x 220 x 160 mm @ 2.5 x 2.5 mm resolution, duration = 14:00 minutes). Images will be analyzed using open-access neuroimaging tools and custom MATLAB scripts, including FreeSurfer v7.3.2 for whole-brain morphometric analysis, including hippocampal subfields, and FSL v6.0 for BOLD fractional amplitude of low frequency fluctuation and resting-state functional connectivity. FDG PET computed tomography (CT) imaging will evaluate patterns of hypometabolism. FDG PET brain examination shall be performed as per SNMMI/EANM guidelines. The participants will be required to fast for 4 to 6 hours and a blood glucose test will be measured before administration of FDG. A cutoff blood glucose level < 8.9 mmol/L (< 180 mg/dL) will be used. Approximately 5 mCi of FDG will be administered intravenously and after an uptake time of 30 to 60 minutes in a quiet and dimly lit room, a 10 minute 3D mode PET static acquisition and low dose CT of the brain using a General Electric (GE) Discovery MI PET CT scanner will be performed. The images will be processed and reviewed on GE Advantage Window workstation using CortexID Suite application.

2.3.9 | Retinal imaging

Participants will be invited to take part in a non-invasive optical imaging technique aimed at identifying retinal plaques. Optical retinal imaging methods allow for the early identification of retinal plaques, even before they become detectable in the brain. Furthermore, the accumulation of retinal plaques correlates with the progression of the disease.[39] The present study will explore the relationship between measures of retinal amyloid plaques and other biomarkers quantified in neuroimaging and fluid biomarker procedures, as well as socioeconomic, neuropsychological, and clinical health and lifestyle data. Participants who meet eligibility for the study will be invited to take part in the retinal imaging visits. The participants who elect to take part will be screened for additional exclusion criteria for this imaging procedure (see Table 1). The visit involves monochromatic imaging, which captures images of the eye using only one specific wavelength or color of light. The fluorescence microscope or scanner will be used to capture the emitted fluorescent light from the retinal targets (plaques). A safety assessment by a physician investigator after completion of retinal imaging and prior to leaving the clinic will be conducted at each visit.

2.3.10 | Physiology

Participants will be invited to fit wearable consumer sensors (FitBit Inspire 3) to their wrist for 14 days that include a three-axis accelerometer, red and infrared blood oxygen (SpO2) sensor, ambient light sensor, and optical heart rate monitor to continuously and passively monitor and classify physical activity, sleep, and autonomic function and stress responses.

2.3.11 | Hearing loss, tinnitus, and vision

We will use the Whispered Voice Test to detect hearing impairment among our study participants. In this test, the examiner gives a number-letter-number combination, that is, 8-M-3, K-5-R, 2-J-7, and S-4-G. If the participants repeat the letters and numbers correctly it is considered a pass.[40] Furthermore, we will be using a tinnitus questionnaire to assess prevalence of tinnitus in the Kenyan population as well as its association with dementia risk, as found in previous studies (see Yang et al.[41] for a meta-analysis). To assess near and distance visual acuity, we will use the WHOeyes app.[42] Study participants will be evaluated on their ability to identify and distinguish objects or letters at specified distances. Visual impairment will be determined based on visual acu-

ity. For near vision impairment, we will consider a visual acuity worse than N6 or M.08 at 40 cm. For distance vision impairment, we will use the following: (1) mild—visual acuity worse than 6/12 to 6/18, (2) moderate—visual acuity worse than 6/18 to 6/60, (3) severe—visual acuity worse than 6/60 to 3/60, (4) blindness—visual acuity worse than 3/60.

2.4 | Secondary data

Presence of the following secondary data about health conditions will be extracted from the medical records of the participants with MCI and AD and will be recorded, using ICD-10-CA diagnosis codes: congestive heart failure, cardiac arrhythmia, vascular disease, pulmonary circulation disorders, peripheral vascular disorders, chronic pulmonary disease, hypothyroidism, HIV/AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, liver disease, renal failure, rheumatoid arthritis, coagulopathy, fluid and electrolyte disorders, deficiency anemia, hemochromatosis, Wilson's disease.

2.5 | Statistical approach

2.5.1 | Power analysis

Power calculations are based on case–control analysis of cognitively unimpaired and impaired participants from the Ibadan dementia study population of similar African ancestry.[43] A sample size of 250 (i.e., 60 AD, 40 MCI, and 150 controls) is estimated as sufficient for FemBER-Africa, based on a priori estimates from pilot data in a Nigerian cohort which found male sex as a significant factor associated with lower AD risk (HR: 0.49, 95% confidence interval: 0.36–0.67). The group numbers exceed the minimum of 80 subjects ($n = 40$ per diagnostic group of CU and AD) needed to detect a significant mean difference (0.56) in global cognition across sex and diagnostic (AD vs. CU) groups, with 80% power using a two-sided 5% level test. Study results from our feasibility project will inform effect size estimations for fully powered subsequent longitudinal studies. Specifically, preliminary data on cognitive performance, biomarker distributions, and subgroup variability (e.g., by sex, menopausal status, or *APOE* genotype) will guide accurate power calculations and sample size planning for future phases. This will enable us to design longitudinal follow-up studies with sufficient statistical power to detect changes over time, assess progression from MCI to dementia, and evaluate the predictive utility of sex-specific, endocrine, and lifestyle factors. In this way, the current cross-sectional phase serves both as a proof of concept and a critical foundation for scaling up Africa-led ADRD research infrastructure.

2.5.2 | Statistical analysis plan

The primary outcome is a global composite based on cognitive domains—memory, executive functioning, visuospatial, language, processing speed. Cognitive impairment is based on performance on at least two neuropsychological measures that are $z \leq -1.5$ (mild) or $z \leq -2.0$ (moderate) lower than a local age-matched normative reference group (currently being collected). Clinical outcomes include diagnostic category (e.g., MCI and AD) diagnosed via standard procedures at the AKU Neurology clinic, which involve cognitive evaluations, clinical lab assessments, brain MRI, and PET alongside CSF biomarkers where required. AD pathology outcomes of interest are CSF/PET Aβ42/tau brain load, MRI regional volumetric and functional network measures, specifically hippocampal volume, cortical AD signature volumes, and resting-state functional connectivity. Primary exposure is sex assigned at birth, gender identity, and reproductive parameters. Secondary outcomes include: cognitive domains (memory, executive functioning, processing speed); functioning level; individual and composite lifestyle/health factors, such as cardiovascular and metabolic risk factors, physical activity, depressive symptoms, sleep, stress-related symptoms, and resilience factors. Exploratory outcomes include: 60 participants (30 AD, 30 CU) included in the FemBER-Africa study will be classified into AD biomarker positive and negative groups based on the 2018 National Institute on Aging–Alzheimer's Association guidelines. These subjects will undergo brain MRI (e.g., volumetry, cortical thickness, and white matter lesions), cerebral glucose metabolism on FDG PET, and presence of amyloid and tau pathologies via CSF biomarkers. All 250 participants will undergo ophthalmologic evaluations and AD-related blood-, saliva-, and hair-derived markers (e.g., Aβ40/42, p-tau217, neurofilament light polypeptide).

Regression models (linear/logistic) will assess linear and nonlinear associations between exposures and outcomes, adjusting for confounders (e.g., site, age, sex, resilience, social factors). Subgroup analysis (age, sex, and ethnicity) and qualitative feedback will refine the protocol. Dementia risk scores will be computed using phenotypic data, with sex-based effect modification. Feasibility of novel technologies (e.g., digitized assessments, non-invasive sampling) and data collection methods will also be evaluated.

2.5.3 | Ethics and regulatory requirements

We have AKU ethical approval (2023/ISREC_121) and a National Commission for Science, Technology & Innovation permit (NACOSTI/P/24/41790) in place to collect data. Participants will provide informed consent following Kenyan regulations and the Declaration of Helsinki. The consent form will outline the study's purpose, procedures, and time commitment. Participation is voluntary, and withdrawal will not affect clinical care. Data collected before withdrawal will be retained for analysis. Identifiers will be removed from data and biospecimens for future research. Participants will be compensated for time and travel. Contact details for inquiries will be provided. Confidentiality will be ensured through a password-protected Brain Health Registry in compliance with Good Clinical Practice and data protection standards.

3 | DISCUSSION

Current ADRD prevention models are primarily based on Western cohorts, limiting their relevance for African populations, especially women, with distinct genetic, hormonal, and socio-cultural risk factors. The FemBER-Africa project addresses a significant gap in global ADRD research by focusing on African populations. This study represents a step toward understanding the complex interaction among sex, ancestry, and socio-cultural determinants of dementia risk.

3.1 | Progress to date and lessons learned: co-designing the biopsychosocial battery

Focus-groups (FGs) with community members have yielded valuable insights that have enhanced the cultural sensitivity and methodological rigor of our study. In response to concerns regarding cultural sensitivity and rapport development, we refined the phrasing and strategic placement of sensitive questions, particularly those related to fertility and reproductive health, to foster trust and improve participant comfort. This adjustment was crucial for eliciting more accurate and meaningful responses. Our FGs also highlighted the importance of understanding traditional fertility and reproductive health practices, such as the use of herbal remedies. We integrated these insights to provide a more comprehensive and culturally grounded understanding of reproductive health behaviors for both women and men. Under the linguistic and cultural adaptation of cognitive and psychosocial measures, we found that despite a thorough translation process, certain Swahili instructions required further clarification to capture subtle linguistic nuances. This was especially true for cognitive measures, for which some original terms were unclear to focus group members. We incorporated their suggestions to improve the clarity and relevance of instructions, enhancing the accuracy and validity of the assessments even further. These lessons have strengthened the cultural adaptability of our study, ensuring more accurate data collection and greater participant engagement.

3.2 | Methodological strengths and challenges

FemBER-Africa's rigorous methodological framework, including harmonization wherever possible with Western and Latin cohorts, enables cross-population comparisons and greater generalizability of findings. The study's co-design with local Kenyan communities ensures cultural relevance and acceptance of cognitive and psychosocial assessments. However, the limited availability of neuroimaging and biomarker analysis infrastructure in Africa presents logistical challenges. Establishing in-country processing and analysis capabilities is essential for sustainable ADRD research in Africa. While currently a cross-sectional observational study, our long-term ambitions are to develop a longitudinal research framework that includes other African countries to build upon capacity for ADRD research across the continent. While the scope of this study is deliberately ambitious this comes with practical trade-offs. We acknowledge the potential respondent burden, particularly for older adults with multiple assessments scheduled in a single visit. The study team has prioritized culturally adapted and field-feasible tools, streamlined where necessary following community consultation. Several components, including biomarker and neuroimaging analyses, are powered for exploratory rather than definitive analyses. As such, we caution that interpretation of subsample data may be limited by sample size or assay reliability. These feasibility insights will be critical in informing refinement of tools and workflows for future longitudinal phases.

3.3 | Public health and global research implications

By identifying sex-, gender-, and ancestry-specific contributors to ADRD, the FemBER-Africa study will inform targeted prevention and intervention strategies tailored to African populations. The study's insights into hormonal, genetic, and lifestyle determinants of ADRD will contribute to more equitable global dementia prevention efforts. FemBER-Africa will draw on the Brain and Mind Institute's Living Lab model to ensure its findings are rapidly translated into policy and practice in real-world settings. This framework is anchored in community co-creation, whereby local stakeholders engage in FGs and "town halls" to inform the development of culturally adapted screening tools, interventions, and other resources. Through iterative feedback loops, community members help refine these materials, enhancing both their relevance and potential for adoption.

Building on these grassroots insights, the project team will deliver targeted policy briefs and convene stakeholder dialogues with ministries, non-governmental organizations, and professional bodies. By presenting data-driven recommendations that explicitly incorporate community priorities, the study aims to guide more equitable resource allocation and strengthen dementia services across diverse African contexts. Finally, FemBER-Africa will compile open-access materials designed for broad dissemination among educators, health-care workers, and the general public. This approach will facilitate adaptation and scale-up in other low-resource settings, ensuring that the study's outputs are translated into tangible, community-led improvements in brain health policy and practice.

4 | CONCLUSION

FemBER-Africa is a landmark effort to address ADRD research gaps in Africa. By integrating biological, lifestyle, and socio-cultural factors, it will generate sex- and gender-informed insights with global relevance. The protocol establishes a foundation for scalable, Africa-led dementia prevention science, while highlighting key feasibility and cultural considerations. Although some components are exploratory and respondent burden must be carefully managed, this phase will yield

valuable data and implementation lessons to inform future longitudinal prevention research.

AUTHOR CONTRIBUTIONS

Conceptualization: Chinedu T. Udeh-Momoh and Tamlyn J. Watermeyer; investigation: all authors; methodology: all authors; project management and operational oversight: Linda Khakali, Catherine Onyancha and Nyambura Njogu; scientific oversight: Chinedu T. Udeh-Momoh and Tamlyn J. Watermeyer; writing—original draft: Tamlyn J. Watermeyer; writing—review and editing: all authors.

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CONFLICT OF INTEREST STATEMENT

S.G. is an employee of Scottish Brain Sciences, an independent research organization, and the University of Edinburgh. Scottish Brain Sciences was not involved in the design, analysis, drafting, or review of this work. J.S.Y. serves on the scientific advisory board for the Epstein Family Alzheimer's Research Collaboration and serves as editor-in-chief of *npj Dementia*. All other authors report no disclosures. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

After a brief embargo period, all relevant data from this study will be made available upon study completion through the Alzheimer's Disease Data Initiative platform or similar. Researchers may request access through application to the Chief Investigators for review by the data management executive committee.

CONSENT STATEMENT

All study participants will provide written informed consent in accordance with Kenyan regulations and the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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