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STUDY PROTOCOL

REVISED Prevalence, aetiology, and service mapping of dementia in rural Uganda. *Part of DEPEND Uganda (Dementia Epidemiology, unmet Need and co-Developing Solutions in Uganda).*

[version 2; peer review: 2 approved]

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v2 **First published:** 24 Sep 2024, **9**:544
https://doi.org/10.12688/wellcomeopenres.22944.1
Latest published: 24 Jan 2025, **9**:544
https://doi.org/10.12688/wellcomeopenres.22944.2

Abstract

Background

Dementia prevalence in low- and middle-income countries is increasing, yet epidemiological data from African populations remain scarce. Crucial risk factors differ in Africa from more intensively studied global areas, including a higher burden of cerebrovascular disease and HIV, but lower rates of other risk factors like physical inactivity.

Understanding dementia aetiology in African settings has been limited by the expensive and invasive nature of biomarker testing. This study leverages developments in blood-based and retinal imaging biomarker technology to examine the drivers of dementia in older Ugandans.

People with dementia have complex needs benefiting from multi-dimensional support. Understanding current services will allow identification of barriers and opportunities to strengthen support

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 24 Jan 2025	✓ view	✓ view
version 1 24 Sep 2024	✓ view	✓ view

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Any reports and responses or comments on the article can be found at the end of the article.

available to people with dementia and their families.

Methods

The study is nested within the General Population Cohort run by the Medical Research Council/Uganda Virus Research Institute & London School of Hygiene and Tropical Medicine Research Unit. All adults aged 60+ (around 1400) are undergoing brief cognitive screening.

In Part 1, cohort participants are selected based on screening scores to undergo detailed cognitive assessment, using methods developed by the 10/66 Dementia Research Group.

Part 2 is a case control study of people with and without dementia using antecedent data, questionnaires, physical assessment, retinal imaging, and Alzheimer's blood-based biomarkers. We will also compare disability, frailty, quality of life, and social engagement in people with and without dementia.

Part 3 assesses current formal support structures for people with dementia through review of publicly available literature and expert interviews.

Conclusions

This is the first study in Africa using blood-based and retinal imaging biomarkers to examine pathological processes underlying dementia, and systematically map services available for people with dementia. This paves the way for effective policy strategies and further focused research regarding both dementia prevention and support for affected people and their families.

Plain language summary

The number of people experiencing dementia in low- and middle-income countries is increasing. However, there is little information from African countries examining how common dementia is and its causes. Data from high-income countries suggest that the most frequent brain changes linked to dementia are those associated with Alzheimer's disease and blood vessel damage (cerebrovascular disease). Their identification has historically needed advanced scans and lumbar punctures which are very expensive and not always acceptable to people. This study uses new ways to examine brain changes including blood tests and photographs of the back of the eye (retina).

People with dementia have complex needs best addressed by a team of health and social care professionals. To strengthen this support, we need to understand the services currently available to people with dementia.

This study is based within a repeated survey of a population in Uganda called the General Population Cohort (GPC), including around 1400 adults aged 60+. All participants will be given a brief memory test, and based on their scores, a subgroup will undergo a detailed assessment and an interview with someone who knows them well, to look for dementia.

We will compare people with and without dementia to look at dementia risk factors and brain changes using existing GPC data, questionnaires, physical assessments, blood tests and retinal photography.

Furthermore, we will be assessing the support currently available for people with dementia through a review of publicly available data and expert interviews.

This will be first study in Africa to look for brain changes associated with dementia using blood tests and retinal photography, which will inform effective policy strategies for dementia prevention. We will also carry out the first systematic mapping of services available for people with dementia in Uganda: a crucial step towards strengthening them.

Keywords
Dementia, Alzheimer's, epidemiology, Africa, Uganda, prevalence, aetiology, biomarkers

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Author roles: Prynn J: Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft Preparation; **Alinaitwe R**: Methodology, Writing – Review & Editing; **Kimono B**: Project Administration, Writing – Review & Editing; **Peto T**: Methodology, Writing – Review & Editing; **Ashton NJ**: Methodology, Writing – Review & Editing; **Steves CJ**: Methodology, Supervision, Writing – Review & Editing; **Mugisha J**: Funding Acquisition, Methodology, Supervision, Writing – Review & Editing; **Prince M**: Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Wellcome [223492/Z/21/Z].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Prynn J, Alinaitwe R, Kimono B *et al.* **Prevalence, aetiology, and service mapping of dementia in rural Uganda. *Part of DEPEND Uganda (Dementia Epidemiology, unmet Need and co-Developing Solutions in Uganda).* [version 2; peer review: 2 approved]** Wellcome Open Research 2025, **9**:544 https://doi.org/10.12688/wellcomeopenres.22944.2

First published: 24 Sep 2024, **9**:544 https://doi.org/10.12688/wellcomeopenres.22944.1

REVISED **Amendments from Version 1**

1) We have updated the title of the paper to increase impact.

2) We have added a more detailed description of the study setting and population.

3) We have clarified our approach to dementia diagnosis, including clinical validation of at least the first 25 probable cases identified using the 10/66 diagnostic algorithm.

4) We have included more detail about the exposures of interest in the case control study and how they will be assessed.

5) We have updated the description of the data analysis plans to include our approach to missing data, more detail on the PAF calculations, and an approach to assessing bias when calculating the validity of the screening tools for dementia.

Any further responses from the reviewers can be found at the end of the article

Acronyms and abbreviations

AD	Alzheimer's Disease
ADNC	Alzheimer's disease neuropathological change
AVR	Arteriole-to-venule ratio
CRAE	Central retinal arteriolar equivalent
CRVE	Central retinal venular equivalent
CSF	Cerebrospinal fluid
CSID	Community screening instrument for dementia
DBS	Dried blood spots
GFAP	Glial fibrillary acidic protein
GMS	Geriatric mental state
GPC	General Population Cohort
HAND	HIV-associated neurocognitive disorder
HIV	Human immunodeficiency virus
LMIC	Low- and middle-income countries
MRI	Magnetic resonance imaging
NFL	Neurofilament light
NGO	Non-governmntal organisation
OR	Odds ratio
PAF	Population attributable fraction
PET	Positron emission topography
p-tau	Phosphorylated Tau
SD	Standard deviation
SPPB	Short physical performance battery
STRIDE	Strengthening Responses to Dementia
VaD	Vascular dementia
WHO	World Health Organisation
WOPS	Wellbeing of Older People Study

Introduction

Dementia has a profound effect on individuals, families, health systems, and societies and is a leading contributor to disability among older people in low- and middle-income countries (LMIC)[1]. It is estimated by the World Health Organisation (WHO) that the number of people living with dementia will more than double globally between 2017 and 2050, mainly driven by increasing numbers in LMIC[2].

Dementia prevalence data from African settings is scarce

It is imperative to understand the scale of the burden of dementia to consider its impact on the population and how to address it. However, prevalence data from African settings remain scarce.

Early estimates of dementia prevalence in sub-Saharan Africa were from Ibadan, Nigeria in the 1990s, where prevalence was notably lower than in a comparable population of African-Americans in Indianapolis, USA[3]. Since then, more data have emerged which were summarised in a systematic review and meta-analysis in 2017, showing that age-specific prevalence of dementia appeared comparable to prevalence figures across global regions, with 1.7% of people aged 60–64 experiencing dementia, rising to 23.3% of people aged 95+[4]. The review included all population-based studies in adults aged 60+ within sub-Saharan Africa and found 12 studies undertaken in 6 countries.

Since then, a population study of 400 adults over 60 in South-West Uganda in 2020 estimated that 20% had dementia[5]. Participants were assessed using the Brief Community Screening Instrument for Dementia (Brief CSID), but no detailed cognitive testing or diagnostic assessment was done. The authors used previously published sensitivity and specificity data of the screening tool derived from populations in Latin America, China, India, and Nigeria[6] to back-estimate the likely dementia prevalence. In Northern Uganda in 2023, another study also used the Brief CSID in a population-based survey of 434 adults over 50, and estimated a prevalence of 23% of possible or probable dementia[7]. These estimates, based solely on brief screening tools, are higher than expected based on other regional data[4] Further investigation using in-depth cognitive, psychological and physical assessments is crucial to explore these findings, and understand the underlying drivers of dementia in Ugandan populations.

Risk factors and aetiology of dementia may differ in African populations compared to other global regions

Dementia risk factors

Fourteen key potentially modifiable risk factors have been identified for all-cause dementia: low educational attainment, midlife hypertension, midlife obesity, hearing loss, smoking, depression, physical inactivity, social isolation, diabetes, air pollution, excessive alcohol consumption, traumatic brain injury,

high low-density lipoprotein cholesterol and untreated vision loss[8]. Worldwide, 45% of dementia cases are estimated to be attributable to these factors. However, this is based on data mainly from high-income settings, and assumes both similar strengths of association between individual risk factors and dementia, and prevalence of each risk factor in less comprehensively researched populations. While studies in African settings have demonstrated links between lower educational attainment, vascular risk factors, and social isolation with dementia[5,9–13], data is minimal on other risk factors particularly midlife obesity, alcohol, depression, hearing loss and traumatic brain injury.

Pathological processes leading to dementia

Most people with dementia have multiple contributory pathological processes. Of these Alzheimer's disease neuropathological change (ADNC) is the process with the highest prevalence, followed by vascular changes[14].

Alzheimer's disease neuropathological change (ADNC) is characterised by the presence of amyloid and phosphorylated tau (p-tau) in the brain, which when associated with clinical dementia is Alzheimer's disease (AD). AD is considered a progressive neurodegenerative condition and ADNC changes start many years before symptom onset[15]. It has been suggested that AD is 60–80% heritable, particularly through the APOE4 genetic pathway[15]. However, these estimates are based on data almost exclusively from populations of European ancestry. Because of this, and the wide genetic diversity within Africa, the extent of genetic vulnerability is less clear among individuals of African ancestry[16]. People with ADNC but without clinical dementia are sometimes considered in a pre-dementia stage[17], but the progression to dementia within a given timeframe is not guaranteed, and the factors influencing resilience to these changes are not yet well understood[14]. Validated biomarkers for ADNC used in clinical and research settings in high-income countries include characteristic magnetic resonance imaging (MRI) findings, amyloid-PET and tau-PET scanning, and CSF-biomarkers for amyloid β1–40, amyloid β1–42, phosphorylated-tau 181 and total tau[15].

Dementia associated with vascular changes, including infarcts, small vessel disease, and micro-bleeds secondary to amyloid angiopathy is known as Vascular Dementia (VaD)[18]. Risk factors align with other vascular pathological processes, including smoking, hypertension, diabetes, and hypercholesterolaemia. Diagnosis is supported by signs of cerebrovascular disease on MRI[18]. There is increasing recognition that ADNC and cerebrovascular disease commonly co-exist, particularly in the oldest age groups[14], and may synergistically impact cognition[19].

Multiple other pathological processes also contribute to dementia, including α-synuclein neuronal inclusions (a prominent feature of Lewy Body dementias)[20], tauopathies other than those seen in ADNC, and neuronal inclusions of TAR DNA-binding protein 43 (TDP-43)[14]. Furthermore, neuroinflammation and cellular ageing mechanisms are increasingly considered important drivers of neurodegeneration[14], and active ongoing research in this field is likely to uncover more processes.

In the pre-antiretroviral era, HIV-associated neuro-cognitive disorder (HAND) was commonly seen with HIV infection[21]. However, understanding whether chronic and well-controlled HIV impacts cognition with ageing is challenging, due to difficulties disentangling the effects of comorbidity and ART[22], and a paucity of studies in older people. However, HIV infection has been linked to accelerated biological ageing[23], increased incidence of Alzheimer's disease[24], and vascular complications[25].

Little is known of dementia drivers within Africa, as studies characterising dementia subtype have relied on clinical criteria[26–28], which have poor diagnostic accuracy compared to neuropathological examination, the gold standard[29,30]. From limited data, it is suggested that cerebrovascular disease may be a greater contributor to dementia in Africa than other global regions[16,31]. This is plausible due to a high burden of stroke seen in many African settings[32], and a high prevalence of undiagnosed and untreated vascular risk factors[33,34]. This urgently needs clarifying as it implies that dementia incidence may be substantively reduced with improved control of vascular risk factors.

This study takes advantage of recent scientific advances in biomarkers for ADNC and cerebrovascular disease allowing identification of these processes, without the need for prohibitively expensive or invasive neuroimaging and CSF biomarker analysis[17].

Novel diagnostic biomarkers enable identification of pathological processes leading to dementia

Blood based biomarkers for Alzheimer's disease neuropathological change

Thanks to the development of new high-sensitivity assays, biomarkers for ADNC previously only accessible in cerebrospinal fluid (CSF) are now detectable in blood at much lower concentrations[35]. Amyloid beta and phosphorylated tau (p-tau) concentrations are highly correlated with the well-established CSF and PET biomarkers of ADNC, while neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) are informative biomarkers of neurodegeneration[35]. Using a panel of biomarkers will enable us to identify participants with ADNC, and distinguish AD from other neurodegenerative processes in participants with clinical dementia. Furthermore, recent technological advances have enabled identification of biomarkers from dried blood spots (DBS). This is a highly promising option where access to cold-chain for sample storage and transportation is limited or lacking,[36].

Retinal imaging for cerebrovascular disease

Changes in the retinal vasculature are very highly correlated with cerebral vasculature, due to shared anatomical and physiological properties of the brain and retina[37]. Recent advances in semi-automated and automated analysis of retinal vascular morphology allow retinal imaging to act as a proxy

for direct brain imaging to identify cerebrovascular disease[38–40]. The measures of interest are retinal vessel calibre changes, specifically the central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), and their relationship – the arteriolar-venular ratio (AVR) - as well as quantification of tortuosity and fractal dimension of vessels[41]. This is a highly novel and promising option for identification of cerebrovascular disease in remote or low-income settings.

People living with dementia in Uganda have unmet health and social care needs

Dementia is among the most important causes of disability and care needs for older people in LMIC[1,42–44], and is associated with stigma and social isolation[16,45]. People experiencing dementia have complex needs that benefit from multi-dimensional support including medical input for diagnosis, support with advanced care planning, caregiver support, and therapeutic interventions to promote ongoing independence[46,47].

However, there is a significant gap between this demand and the provision in many LMIC, including in Africa[48]. Qualitative work with healthcare providers in southwestern Uganda showed that while clinicians with specialist mental health training felt confident in diagnosing and managing dementia, many other healthcare workers felt ill-equipped to assess people with dementia, while some believed that dementia symptoms were a normal part of ageing[49].

Caregivers of people with confirmed dementia in Uganda reported multiple contacts with healthcare prior to receiving a diagnosis, and most had presented to healthcare for related problems (such as pressure ulcers or seizures) rather than the cognitive impairment. They also described the high cost of medication and investigations, requiring selling of assets[50]. Caregivers reported feeling unsupported in understanding how best to care for the person with dementia[51]. Understanding the conformation and function of current services will allow identification of barriers and opportunities for strengthening the support available to people with dementia and their families.

This study will be partnered with a study investigating the experiences and unmet needs of people with dementia and their caregivers within the same community using qualitative methods.

Aims and objectives

Aim

To increase understanding of the epidemiology of dementia in Uganda, and work towards a strategy for risk reduction and improving outcomes and care.

Objectives

Within a rural Ugandan population to:

1) Evaluate the prevalence of dementia.
    a. What is the prevalence of dementia in adults aged 60 and over within one rural Ugandan population?
    b. What is the prevalence of dementia among people aged 60 and over living with HIV?
    c. What is the sensitivity and specificity of the WHO-recommended cognitive screening tools for dementia?
2) Establish the causes and associated factors of dementia to inform risk reduction strategies.
    a. What is the association of socio-economic position, education, cardiovascular risk factors, and HIV with dementia?
    b. What is the relative importance of Alzheimer's disease compared to cerebrovascular disease and other dementia causes in this setting?
    c. Can venous and capillary DBS be used to accurately assess Alzheimer's disease biomarkers in a rural Ugandan setting?
3) Understand the formal support available for people living with dementia and their families.
    a. What medical diagnostic and treatment services are available and accessible for people living with dementia?
    b. What social care and support services are available for people living with dementia and their families?
    c. What financial support is available for people living with dementia and their families?

Protocol

Study design

There are three parts to this study.

Part 1: Cross-sectional survey to understand the prevalence of dementia.

Part 2: Nested case control study to understand the risk factors and underlying pathological processes leading to dementia and its associated factors, with a cross-sectional analysis frailty, disability, and quality of life of older people with and without dementia.

Part 3: Situational analysis of the formal care and support context in which people with dementia and their caregivers are living. This will include:

1) A desk review of information available in the public domain.
2) Qualitative semi-structured interviews with dementia experts.

Study setting

Uganda is a diverse country with more than 65 recognised tribes and a population of just under 50 million[52]. This study is

based within the rural Kalungu District of Kyamulibwa Sub-county in south-western Uganda, where the large majority of the population are from the Buganda tribe, and speak Luganda as a first language. The national life expectancy at birth is 69.3 years[53], and when last estimated in 2014, life expectancy at age 69 was 79.5 years[54]. An estimated 3% of the population are aged 60 or over[52].

The study is nested within the existing **General Population Cohort (GPC)** at MRC/UVRI & LSHTM Uganda Research Unit (MUL). This is an open cohort that was established in 1989 with follow-up every two years, and comprises all residents of a sub-county of Kalungu District[55]. At the last census round in 2021–2023, there were around 1400 adults aged 60+.

Data are routinely gathered on socio-demographics, medical history, lifestyle, anthropometry, blood pressure, and HIV status. At the current round of data collection, which started March 2024, for people aged 60 and over the data collected includes cognitive screening, which is performed using WHO-recommended tools:

- Verbal fluency: number of animals named within one minute.
- Immediate and delayed verbal recall of 10 words.
- Digit span: recalling increasing numbers of digits forwards and backwards.

We will use existing cognition data from the **Wellbeing of Older People Study (WOPS)** to estimate local population norms for these screening tests. WOPS is a population-based cohort enriched for HIV+ participants that was established in 2009 and includes participants from Kalungu District as well as from Masaka town and Wakiso District (near Entebbe). It comprises around 500 adults over 60, of whom 50% were HIV+ at the time of recruitment[56]. In addition to socio-demographic and health questionnaires, cognitive screening is performed using the WHO-recommended tools that have recently been introduced into the GPC. As the WOPS population is not population-representative, the mean and standard deviations (SDs) will be adjusted to the socio-demographic distribution of the underlying population using inverse probability weighting.

Part 1 – Cross-sectional survey to understand the prevalence of dementia

Population

The study population will be adults aged 60+ from the GPC cohort, selected based upon their cognitive screening results. We aim to recruit all of those with impaired cognition at screening (a score lower than the cutpoint of 1.5 SDs below the mean), a random sample of 50% of those with mildly impaired cognition (a score between 1 and 1.5 SD below the mean), and a random sample of 15% of those with unimpaired cognition (a score higher than 1 SD below the mean). We will ask the older person to identify an informant: someone who knows them well and if relevant, cares for them, to share their experience of the older person's cognition and behaviour. We do not know of any residential or social care facilities for older people within this District, thus we anticipate that all older people living with dementia will be living in the community.

Sample size

Around 300 older people will have in-depth cognitive assessment based on their performance at screening tests. In view of the two-phase sampling design, the precision of the prevalence estimate will depend on the sensitivity and specificity of the screening tools, which is yet to be determined.

Procedures

Participants will be recruited on a rolling basis while GPC data collection is ongoing, based on their score at cognitive screening.

Older people and informants will be approached to participate in their homes by Luganda-speaking interviewers. The purpose of the study will be explained and informed consent sought. More detail on consent procedures can be found in the Ethical Considerations section. Participants will also be asked at this stage whether they would want to be informed of a dementia diagnosis if it was made based on these assessments.

If participants are not at home at the time of the visit, we will make at least 2 further attempts to contact them at different times of day.

Their cognitive assessment will be done using the following three tools:

1) Community Screening Instrument for Dementia (CSI-D)

The includes assessment of cognition across multiple cognitive domains, and an informant account of the older person's cognition and function, including whether there has been any deterioration in cognition. It was developed specifically for use in diverse lower-literacy populations, and has been used across the world in multiple settings, including in Africa[57].

2) Modified Consortium to Establish a Registry of Alzheimer's Disease (CERAD) 10-word list-learning test with delayed recall

This is a widely used tool for assessing cognition and has shown minimal bias across different cultural contexts[58,59].

3) Geriatric Mental State (GMS)

This assesses the older person for clinically significant mood disorders (depression and anxiety), and psychosis as well as cognition, integrating this information algorithmically to generate a probable principal diagnosis.

Combining the output of these three measures to generate a diagnosis of probable dementia was pioneered by the 10/66 Dementia Research Group, who developed an algorithm validated against psychiatrist diagnosis of dementia in multiple global regions including Africa[60] which is publicly available

on the 10/66 Dementia Research Group website[61]. The methods have been extensively used across the world, and have shown good predictive validity in cohort follow-up[62]. As these tools have not previously been used in Uganda, we will review the tools with the study advisory group prior to starting data collection, and pilot rigorously with older people from the WOPS cohort to ensure the tools are acceptable and appropriate to this setting, as described later.

The whole assessment will take between 50 and 90 minutes, depending upon the extent of morbidity, and any communication difficulties. Interviews will be held in a quiet private space where possible, for both confidentiality of the participants, and, by avoiding distractions, to maximise their performance in cognitive testing. For participants unable to complete the entire assessment, data are captured within the GMS to help determine the likely reasons for non-completion (such as memory loss, communication difficulties, incoherence), and these data are included in the algorithmic diagnosis of dementia.

To ensure that these cognitive assessment tools are accurately identifying dementia, at least the first 25 cases identified will also undergo a clinical review by a doctor experienced in dementia diagnosis. If concordance between clinical review and the 10/66 tools is high, then the remaining cases will be identified using the 10/66 tools as they are. Otherwise, we will assess the elements driving any discordance and try to adapt the diagnostic process to increase validity of the tool. If necessary, all potential cases can undergo a clinical review to confirm eligibility as cases prior to allocation to the case control study.

Analysis plan

Dementia prevalence will be presented as the percentage of the GPC population with dementia, with 95% confidence intervals[63]. This will be calculated using weighted logistic regression accounting for the two-phase sampling methodology[64].

The WHO-recommended screening tools will be validated against a diagnosis of dementia, calculating sensitivity, specificity, and positive and negative predictive values. We will also assess for bias by sex, years of education, and age group using logistic regression modelling to identify any variables independently associated with screening score once dementia diagnosis is controlled for.

Part 2 – Case control study to understand the risk factors and pathological processes leading to dementia, with a cross-sectional comparison of disability, frailty, and quality of life among people with and without dementia.

Population

We will aim to recruit all participants who have been identified to have dementia in Part 1 as cases. Controls will be all GPC participants who have undergone detailed cognitive assessment at Part 1 who do not have dementia. This is summarised in Figure 1.

Sample size

Recruitment of cases will continue until all scheduled Part 1 assessments have been completed. The total number will therefore depend on the underlying prevalence, the attrition rate of participants between the different study parts, and the sensitivity and specificity of the screening tools. There will be up to four controls per case, depending on the number of cases identified. If prevalence of dementia or participation rates are low yielding few potential cases, we will also recruit participants with low scores at cognitive screening from the WOPS cohort who would then go through the same cognitive assessment procedures, aiming for at least 80 cases in total. If unexpectedly high numbers of people with probable

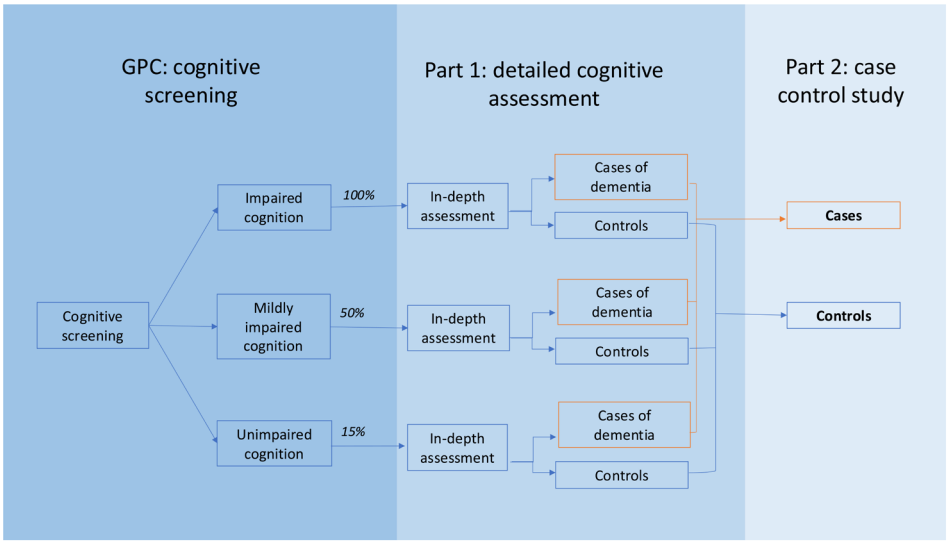


Figure 1. Outline of the stages of recruitment for Part 2 of the study.

dementia are identified, recruitment for the case control study will stop once 200 cases have been identified. Controls would then be selected only from the villages within the GPC population that yielded the cases.

In Table 1, the detectable odds ratio (OR) with 80% power and 95% confidence are outlined for different exposure prevalence levels among controls and an assumed 80 cases of and two controls per case.

Inclusion and exclusion criteria
Cases will be identified based on their assessment in Part 1.

Procedures
Eligible participants will be approached at home to invite them for Part 2, which will be completed at the Kyamulibwa Research Station. For those unable to travel independently, we will provide transport to the centre. Informed consent will be sought, using the same processes as in Part 1. The key exposures in the case control study are summarised below.

- Key risk factors
    - Educational attainment
    - Vascular risk factors including tobacco smoking, obesity, blood pressure and diabetes
    - History of head injury
    - Alcohol excess
    - HIV
    - Social isolation
    - Hearing loss
    - Household air pollution
    - Early life adversity including food insecurity and loss of a parent during childhood
    - Poverty
- Pathological processes
    - Alzheimer's neuropathological change (using blood biomarkers)
    - Cerebrovascular disease (using retinal imaging)

Data on these exposures will be obtained from:

- Antecedent cohort data
- Questionnaires
- Physical assessment
- Blood tests
- Retinal imaging

Questionnaires
Questionnaires for both the older person and their informant will be administered by interviewers in Luganda, which is spoken as a first language nearly universally by residents of this subdistrict.

The questionnaire for participants will include the following elements:

- **Socio-demographic information** – study-specific questionnaire.
- **Dementia risk factors** – study-specific questionnaire covering alcohol intake, early life adversity, vision, hearing, and medical history.
- **Disability** – WHO Disability Assessment Schedule (WHODAS) 2.0 (12-item)[65].
- **Social engagement** – study-specific questionnaire adapted from the WOPS study[66].
- **Quality of life in dementia** – DEMQOL[67].

It is likely that some participants will be unable to reliably answer questionnaires due to cognitive impairment and will require an informant to answer a proxy version of the questionnaire. However, cases and controls must undergo identical procedures to minimise information bias, and interviewers will be masked to whether the participant is a case or a control. Therefore, this approach will not be restricted to cases only: for all participants, informants will also be administered proxy versions of all the older person's questionnaires. At the end of each interview with both the older person and the informant, the interviewer will be asked to subjectively rate their confidence in the reliability of the answers given. Where there is doubt in the reliability of the older person's

Table 1. Power calculation for case control study in Part 2.

Number of cases recruited	Control : Case ratio	Prevalence of exposure among controls	Detectable OR
80	2	50%	2.2
80	2	20%	2.3
80	2	6%	3.3

answers, regardless of whether they are a case or control, and the informant's answers were perceived as more reliable, the informant's answers will be used in place of the older person's answers for the analysis.

Older people should be assisted as much as possible in completing the assessments, including ensuring the use of any eyeglasses or hearing aids that they usually use, and taking breaks as necessary. Communicator headphones will be provided for people with uncorrected hearing impairment.

The questionnaire specifically for informants will include the following elements:

- **Socio-demographic information**: data from previous GPC waves, study-specific questionnaire
- **Care needs of the older person**: study-specific questionnaire adapted from the WOPS study[66]
- **The older person's social participation**: IDEA-IADL[68].
- **Depression and anxiety:** PHQ-9[69], GAD-7[70].
- **Quality of life**: WHOQOL-Bref[71].
- **Presence of behavioural and psychological symptoms of dementia in the older person**: Brief Neuropsychiatric Inventory Questionnaire (NPI-Q)[72].
- **Impact of supporting the older person** (informants identifying as caregivers only): Zarit Burden interview[73].

Physical assessment
Physical assessment of older people will be done using an adapted version of the established NEUROEX tool[63] and includes the following elements:

- Structured neurological examination.
- Gait speed – participants will be timed walking 4 metres.
- Brief dental examination.
- Hearing – using the WHO-recommended Whispered Voice Test.
- Distance vision – using the PEEK application on tablet computers or Tumbling E chart.
- Grip strength

Furthermore, to complete the required elements of the Short Physical Performance Battery (SPPB)[74], we will do the following assessments:

- Chair stand test – the time taken to complete five sit-to-stands.
- Balance test – participants will be timed to test if they can stand for 10 seconds with their feet together, feet in a semi-tandem position, and feet in a full-tandem position with their eyes open.

Blood tests
Blood tests will be done for both cases and controls to look for reversible causes of dementia:

Set 1:

- Full blood count – and if anaemia is present, Vitamin B12.
- Creatinine.
- Thyroid Stimulating Hormone.
- HbA1C.
- Syphilis screening with Rapid Plasma Reagin – if positive, treponemal testing.

Set 2:
Blood will be taken for blood-based Alzheimer's biomarkers:

- Amyloid beta 42 and 40.
- Phosphorylated Tau-217.
- Neurofilament light.
- Glial fibrillary acidic protein.

This involves both a venous blood sample for all four blood-based biomarkers and capillary finger-prick samples for dried blood spots for p-Tau217, NfL, and GFAP. As this is a fast-developing scientific field, this panel may be broadened if other relevant biomarkers are validated during the course of the data collection.

Retinal imaging
Participants will have retinal photography done of each eye using a 3nethra Classic camera to assess the vasculature. Images will be interpreted using automated processes to quantify vascular retinal morphology, including the central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), arteriolar-venular ratio (AVR)[40].

Analysis plan
We will use unconditional multivariable logistic regression to calculate odds ratios for each exposure of interest. This will be adjusted for possible confounders, and account for any clustering at household level, and sampling probabilities in Part 1 of the study.

We will use these data to calculate the population attributable fraction (PAF) for each individual modifiable risk factor and overall, using weighting to account for any communality. This will give an indication of the proportion of dementia cases that could theoretically have been prevented if these risk factors had been completely controlled.

The PAF for each of the pathological processes (Alzheimer's pathology and cerebrovascular disease) will indicate the relative importance of these two processes in the development of clinical dementia in the population studied.

For people with and without dementia, we will compare the older person's quality of life, social engagement, disability, frailty, and quality of life.

We will assess the correlation and agreement between the AD biomarker values in EDTA plasma samples with dried blood spot samples using Spearman rank correlation and intra-class correlation coefficients.

As the study is nested within an established population cohort, we will be able to examine characteristics of people with missing data, including those who were not screened due to non-participation in the GPC, those who were sampled but did not participate in the DEPEND study, and those who participated but not all the required data were gathered. This will help us establish patterns of missingness, and where appropriate, multiple imputation strategies will be used.

Part 3 - Situational analysis of the formal care and support context in which people with dementia and their caregivers are living

Population

In addition to a desk review we will be recruiting key decision-making and topic expert stakeholders for interviews. Potential participants will be approached from the following sectors: health and social care, civil society groups and non-governmental organisations, traditional healing, and government officials, at both regional and national levels, and across geographic regions. They will need to have at least 2 years of experience within their sector to participate. We will identify potential participants through publicly available information on websites and through snowballing methods.

Procedures

We will be using an adaptation of the STRIDE (STrengthening Responses to DEmentia) analysis tool[75] to undertake a thorough situational analysis of the formal care and support landscape in which people with dementia are living in Uganda. This has been developed to allow researchers to gather comparable data across different settings and has already been used in South Africa and Kenya[48,76], among other countries.

1) Desk review

This is a review of data in the public domain to provide a summary of the health system, long-term care system and policy contexts relevant to dementia, as well as dementia awareness and stigma, and social protection for people with dementia specific to Uganda. This is summarised in Table 2.

2) Interviews with experts

This stage involves in-depth interviews on the emerging findings, to gain a more thorough understanding of the experiences of people with dementia and their communities, and the potential routes to developing or scaling-up an evidence-informed care pathway. We will start with around ten participants and increase numbers until saturation is reached.

Interviews will explore how the community conceptualises healthy ageing and dementia, health services available for people with dementia, identification and management of dementia, awareness and prevention, long-term care services, policy prioritisation, and elder abuse. They will make use of vignettes, initially developed by the STRIDE team[75], to represent cases of people developing dementia symptoms in different contexts in Uganda. The aim is to prompt discussion on the likely or possible patient journeys and services available, to identify both the barriers to diagnosis and support, and any examples of best practice.

Analysis plan

Interviews will be digitally recorded and transcribed verbatim. Transcripts will be entered into NVivo software for analysis. We will use a framework analysis approach to code the interview data by pre-defined themes identified through the desk review.

Stakeholder engagement for the DEPEND Uganda project

Prior to starting data collection, we will establish a study advisory group including members of civil society groups such as the Uganda Alzheimer's Association, Uganda-based researchers and/or clinicians with dementia expertise, and older people with and without dementia. We will engage with this group throughout the project, seeking advice and support regarding community-sensitisation, data collection tool development, supporting people diagnosed with dementia through the study, and dissemination of research output.

Translation and piloting

All data collection tools will be translated from English to Luganda using translation/back-translation methods. That is, a translator proficient in English and fluent in Luganda will translate the tools into Luganda. An independent translator proficient in Luganda and fluent in English will back-translate the tools to English. Discrepancies arising between the original tool and the translated/back-translated version will be discussed with both translators to find a consensus. The translated version will then be discussed with the study advisory group.

For the piloting, we will recruit participants and informants from the WOPS cohort with a broad range of scores at cognitive screening at most recent testing, and who are not also in the GPC, as there is some overlap. This will be to check a) how well the questions are understood by participants (including the use of cognitive interviewing techniques), and b) practical elements of the data collection including the duration of the assessments.

Informed consent processes

Participants will be required to give informed consent prior to data collection. It is important for this study that people

Table 2. Summary of the domains covered in the desk review as part of the situational analysis.

Domain	Contents
Overall country context	Population and demographic characteristics Epidemiological situation Economic and social situation Social protection Political situation
Overall health system context	Health system organisation Health system financing Health system workforce
Overview of the long-term care system context	Long-term care system organisation Long-term care system financing Long-term care workforce
Dementia policy context	Governance Dementia policies and plans Legislation Clinical guidelines, standards and protocols for dementia Dementia care co-ordination The policy process
Dementia awareness and stigma	Public awareness and education
Epidemiology and information systems for dementia	Epidemiology Information systems
The dementia care system	Overview of the dementia care system Dementia care system organisation Dementia care system workforce Health and long-term care facilities Antidementia medication and care products
Unpaid care and other informal care for dementia	Informal care workers Family/unpaid care
Social protection for people with dementia	
Dementia research	

without the capacity to consent are not excluded, as people with dementia have the right to contribute to research that may help them or other people with dementia in the future. For participants lacking capacity to consent participation will be agreed with their closest relative or carer and documented on an Informant Declaration Form. If the participant gives any verbal or non-verbal indication of disagreeing with any part of the study, then they will not be included.

Consent will be documented by signing a consent form for those able to write, or a thumb print for those who are not. For people unable to read, this will be witnessed and signed by another community member who is able to read.

Dissemination of findings

Integral to this study is active engagement with the local community and wider scientific and policy-making groups. Our dissemination plan will be made in close collaboration with the GPC Community Advisory Board and the DEPEND Study Advisory Group.

Throughout and following the study, we will hold regular meetings with the GPC Community Advisory Board to update them about the study and publicise its main outcomes. Additionally, we will communicate directly with community members through meetings organised with the support of village leaders.

We plan to communicate the findings of this study with policy makers, researchers, and implementers through the production and dissemination of open-access academic papers in high-impact publications, timely newsletters, and policy briefs. We will invite decision-making and policy stakeholders relevant to dementia and older people's health to a workshop to disseminate the main findings with a focus on the implications for public health and policy.

Data management plan

Questionnaires

The questionnaires will be programmed onto encrypted tablet computers using ODK. This is linked to a central database from previous rounds of data collection, to allow easy identification of participants. After collection, the data will be downloaded from the tablet computers to secure databases on a local project server daily. Data will be regularly backed up and stored offsite on secure servers, without identifiable details. Identifiable details will be held securely by the MUL data management team, and will only be accessed if participants need to be contacted for clinical reasons.

Retinal images

Retinal images will be stored confidentially in encrypted files, labelled with participant ID numbers only. Images and other relevant data (e.g. age, sex, visual acuity) will be shared with external collaborators for analysis will include no identifiable information.

Laboratory Data

Samples will have initial processing at the laboratory at the Kyamulibwa Research Station, then transferred in batches to the MRC-Uganda laboratory in Entebbe for testing.

Samples taken for AD biomarkers will be stored in aliquots, frozen, and subsequently shipped to Sweden for analysis. The freezing facility has a back-up generator to ensure no loss of power and is monitored using an alarm system. Samples sent to remote laboratories for analysis will not have any participant identifiable details, and the process will be covered by a Material Transfer Agreement.

Qualitative data

Interviews will be recorded on a digitally encrypted Dictaphone, and files will be uploaded as soon as possible onto KCL OneDrive labelled with participant ID numbers. The audio file will then be deleted from the Dictaphone. The files used for transcription and translation from Luganda to English will include no identifiable details, but it is possible that the audio content could contain information suggestive of the interviewee's identity. Therefore, any third party involved with transcription or translation will be subject to a strict Data Sharing Agreement to maintain interviewees' confidentiality. Transcript documents will be anonymised and labelled with only broad category of interviewee (e.g. age, sex, role) to give context to their data.

Data sharing

MRC-Uganda is committed to open access data and publications. The data generated will be suitable for sharing as it will be anonymised and may be relevant to a range of different research questions. The Data Sharing Policy will be in line with the Wellcome Trust Policy on Data Management and Sharing.

Once the data sets have been finalised, they will be archived and stored with no identifiable information on the King's Research Data Repository, KORDS for a minimum of 10 years. They will be available to access after findings have been published in an academic journal, and will be accompanied by a codebook metafile providing an accurate description of the content. The concept of data sharing will be included on the participants' consent forms to ensure we have their broad and enduring consent. The Data Sharing Policy will specify that the researchers do not attempt to identify study participants from released data or breach confidentiality in any way, or to make unapproved contact with study participants.

Study protocols, SOPs, and data collection tools will be made freely available after completion of the study.

Impact of the study and future work

This study will provide evidence of the scale and impact of dementia in a Ugandan community, and give insights into the likely experiences of other rural populations across Uganda and Africa more broadly.

Furthermore, modelling of future dementia prevalence and public health planning for dementia risk reduction requires robust data on the causes and drivers of dementia in a specific population, which this study will provide.

This will be the first study to use retinal vessel calibre interpretation and among the first using Alzheimer's disease blood biomarkers in Africa. By extending these non-invasive and hugely valuable techniques into the region, opportunities will be created for much more detailed and accurate research into not only dementia causes and drivers across the continent, but also cardiovascular disease more generally.

Understanding the unmet needs of people with dementia and their carers is the first step in motivating and supporting local, national, and international organisations, and healthcare providers to reach this population. Sensitisation about dementia within the community throughout this project will increase community understanding of dementia as a medical condition, which may cause attitudinal change and increased support for people with dementia and their carers.

This study will pave the way for further work in multiple domains. For example, follow-up of participants would enable assessment of the predictive validity of the dementia diagnostic tools used, as well as prognosis of participants with dementia, incidence of dementia, and future prevalence of dementia. It also provides an ideal platform for interventions, both to support people with dementia and their caregivers, and for participants identified as at high risk of developing dementia in the future.

Ethics and consent

We have been granted ethical approval from the Uganda Virus Research Institute Research Ethics Committee (GC/127/1023) dated 19th July 2024 and King's College London Research Ethics Committee (HR/DP-23/24-42211) dated 30th July 2024. Prior to starting data collection we will also ensure that we

have approvals from the Uganda National Council of Science and Technology and the London School of Hygiene and Tropical Medicine Research Ethics Committee.

Participants will be required to give informed consent prior to data collection. It is important for this study that people without the capacity to consent are not excluded, as people with dementia have the right to contribute to research that may help them or other people with dementia in the future. For participants lacking capacity to consent participation will be agreed with their closest relative or carer and documented on an Informant Declaration Form. If the participant gives any verbal or non-verbal indication of disagreeing with any part of the study, then they will not be included.

Consent will be documented by signing a consent form for those able to write, or a thumb print for those who are not. For people unable to read, this will be witnessed and signed by another community member who is able to read.

Data availability statement

No data are associated with this article.

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Version 2

Reviewer Report 28 January 2025

https://doi.org/10.21956/wellcomeopenres.26103.r117741

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✔ **Sebastian Walsh**
University of Cambridge, Cambridge, UK

Thank you to the authors for considering my suggestions and making alterations to the protocol accordingly. Best of luck with this important research.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dementia; public health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 28 January 2025

https://doi.org/10.21956/wellcomeopenres.26103.r117740

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✔ **Ali G Hamedani**
University of Pennsylvania, Pennsylvania, USA

No further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neurology, neuro-ophthalmology, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 19 October 2024

https://doi.org/10.21956/wellcomeopenres.25264.r103383

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Ali G Hamedani
University of Pennsylvania, Pennsylvania, USA

This publication contains the details of a protocol aimed at studying the epidemiology of dementia in a rural Ugandan population. The motivations for the study are clear, and the literature review is thorough. The study aims and methods are also clearly presented, with only a few minor clarifications needed:

1. Regarding the use of cognitive assessments to ascertain dementia, the authors write that this protocol has previously been validated in the 10/66 study but have not been previously used in Uganda. How are they combined to produce a dementia diagnosis according to the 10/66 study protocol, and how will the validity of this be assessed in the current cohort?

2. The authors describe the stratified sampling strategy for the nested case control study. Aside from the selection probabilities (100% for impaired cognition, 50% for mildly impaired cognition, 15% for unimpaired cognition), how else will the analyses be weighted to be population-representative. For example, if the random 15% of individuals with unimpaired cognition happen to be younger on average than the 85% who were not sampled, how will this be accounted for? Will adjustment for non-response or post-stratification be performed?

3. For the calculations of overall PAF, how will the analyses account for overlapping risk factors (communality)?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neurology, neuro-ophthalmology, epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jan 2025

Josephine Prynn

Many thanks for your comments and queries. We have revised the manuscript and present here the responses to your points:
1. Regarding the use of cognitive assessments to ascertain dementia, the authors write that this protocol has previously been validated in the 10/66 study but have not been previously used in Uganda. How are they combined to produce a dementia diagnosis according to the 10/66 study protocol, and how will the validity of this be assessed in the current cohort? We have clarified that initially the 10/66 algorithm will be followed, and provided a reference for the publicly available algorithm.
Response: We will also be validating the first 25 cases against a clinician diagnosis of dementia. We have re-structured the methods section to make this clearer.

2. The authors describe the stratified sampling strategy for the nested case control study. Aside from the selection probabilities (100% for impaired cognition, 50% for mildly impaired cognition, 15% for unimpaired cognition), how else will the analyses be weighted to be population-representative. For example, if the random 15% of individuals with unimpaired cognition happen to be younger on average than the 85% who were not sampled, how will this be accounted for? Will adjustment for non-response or post-stratification be performed?
Response: If the random sample is not representative of the population, then we can use post-stratification techniques to estimate risk factor prevalence in the underlying population. We have also added a paragraph no handling of missing data and will use sensitivity analysis to explore the potential impact of non-responders.

3. For the calculations of overall PAF, how will the analyses account for overlapping risk factors (communality)?
Response: We will use weighting to account for any communality – the text has been updated to reflect this.

Competing Interests: No competing interests were disclosed.

Reviewer Report 16 October 2024

https://doi.org/10.21956/wellcomeopenres.25264.r103390

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Sebastian Walsh
University of Cambridge, Cambridge, UK

Thank you for inviting me to review this exciting and ambitious proposal for essential dementia epidemiological and services assessment in Uganda, as well as exciting, exploratory biomarker work. This proposal is very well written throughout and very clear. I think the methods are sensible and feasible (though ambitious), including care taken over the appropriate use of informant reports to minimise bias. The author group include relevant expertise of Uganda, dementia epidemiology in LMICs, and biomarkers. Below I offer a few more significant thoughts, and then several minor ones.

MAJOR POINTS:

1. Aims and objectives: A major challenge from the public health perspective of seeing the new biomarkers (and the associated agenda of pushes for earlier diagnosis) transition from being research-useful to clinically-meaningful is demonstrating that they change overall outcomes for the better. I can see from your planned methods and data sources that it is not feasible to design a cohort study to empirically investigate this. But I wonder if you might consider this question within your planned qualitative work. A patient has a set of symptoms and functional needs which are elicited clinically. How does providing a diagnosis (a 'precise' one or otherwise) and how does finding out what their pathology status is affect the treatment and subsequent quality of life of that patient? And do these benefits (assuming there are some) outweigh the opportunity costs of the investment and infrastructure required to deliver the biomarkers routinely? What kind of care pathway is likely to produce the greatest patient/economic benefit at scale? These are questions of relevance globally, but perhaps more so in LMICs where the opportunity costs, even of finger prick or blood-based biomarkers, are likely to be more significant.
2. Missing data: In the analysis plans of parts 1 and 2 I didn't see any thoughts on how any biases through selection, drop out, incomplete reporting (beyond work with informants) will be mitigated or assessed.
3. Retinal imaging. This is not explained in much detail. I can see that this may be a pragmatic alternative to MRI-based assessment of cerebrovascular burden. But perhaps a little more consideration is needed here as to how valid you think retinal imaging is for assessment of cerebrovascular burden (and its spatial distribution through the brain) and associated dementia risk, and to what extent this is really an exploratory (and pragmatic) approach. And in the analysis plan more detail on how you plan to compare the findings of the retinal imaging with the biomarkers. Is it just amyloid pathology and cerebrovascular disease (as measured by retinal imaging) that you plan to include in the PAF calculation? What about the modifiable risk factors? Age?

MINOR POINTS:

Title:
Suggest that you rephrase this for brevity and impact – 'Prevalence, aetiology, and service

mapping of dementia in rural Uganda. A case-control study nested in DEPEND (Dementia Epidemiology, unmet Need and co-Developing Solutions) Uganda.'

Abstract:
Suggest paragraph one, "high" is changed to "higher".
Suggest paragraph four, abbreviations MRC, URI, LSHTM should be spelled out.
Suggest final paragraph you add to the sentence " This paves the way for effective policy strategies for both dementia prevention and support for people with dementia and their families" to include potential for this work to inform research. At the moment you only suggest implications for policy and practice.

Overarching comment:
You use 'prevention' and 'risk reduction' somewhat interchangeably through the manuscript and I wonder if you might go through and select terms more deliberately. Access to antiretrovirals for those with HIV might truly prevent dementia. But addressing the Lancet commission risk factors is likely to have a spectrum of effect and perhaps 'risk reduction' could be more appropriate in this context.

Introduction:
In the Dementia Risk Factors section. The sentence: "Together these factors have been estimated to cause around 45% of worldwide dementia cases." I think the current interpretation of the Lancet commission is that 45% of cases are "attributable" (not 'caused by') the combination of these potentially modifiable risk factors.

In the pathological processes leading to dementia section. The sentence: "AD is considered a progressive neurodegenerative condition which is 60–80% heritable, particularly through the APOE4 genetic pathway[15]". You mention some of this later on, but I think you should mention here, that the APOE work (and all genomic dementia work) has been focused primarily on Caucasian/white European populations, and often in clinical datasets which over-select for younger onset (and therefore presumably higher likelihood of genetic association) cases. Some emerging work has suggested the relationships may be different for different ethnic groups.

This section includes discussion of AD, vascular dementia, and HAND. I think you might add a short additional paragraph after these to mention a) some of the other, rarer causes of dementia (FTD, LBD, reversible forms); and b) that there may be other pathologies which we have not yet fully captured (e.g. recent recognition of the role TDP-43 plays). And other pathological processes, e.g. neuroinflammation, that we haven't fully understood.

Somewhere in the introduction it might be good to include a brief description of Uganda as a place. You reference the provenance of several other pieces of research as being from Northern Uganda or Eastern Uganda. But this might not mean so much to the general reader. Perhaps you could include in this paragraph a very brief note on the demographics of the country as a whole – e.g. what is the life expectancy, median age etc. now, what was it 20, 50 years ago? – OurWorldInData.org is a good source for these kind of data; and also some specific information on the region in focus here (e.g. homogeneity of culture, language spoken, typical occupations, HIV prevalence, typical educational background).

Protocol:

There is mention of stakeholder engagement in part 3 and for dissemination. But I wonder if there is value in initiating this from the outset. Perhaps policymakers and other key stakeholders will have views on what data they need which will add nuance to what data you collect (and how) in parts 1 and 2?

Part 1. Study setting & population. Forgive my ignorance, but are there any social care facilities or similar entities in this part of Uganda where people would reside if there were perceived challenges to them living well at home? As the authors will know, in HICs a key part of dementia epidemiology is a sampling strategy that includes those not residing in the community, but in health or social care facilities. It may well be that this is irrelevant in this region.

Part 1. Population. "We aim to recruit all of those with impaired cognition at screening (defined as ≤1.5 SDs below the mean), a random sample of 50% of those with mildly impaired cognition (≤1 to <1.5 SD below the mean), and a random sample of 15% of those with unimpaired cognition (>1 SD below the mean)". I think all of the greater than/less than signs here are the wrong way round? Please sense check.

Part 1. Analysis plan. I wonder if you might consider analysing whether the sensitivity and specificity of the screening tools differ by participant characteristic. For example, by stratifying the analysis by sex, by years of education (via a binary cut off), by cognitive score, by age, and/or by language spoken or ethnocultural group (if there is heterogeneity in the region).

Part 1. Analysis plan. Please comment on what you plan to do about missing data (e.g. from those not able to complete the 50-90 minute appointment).

Part 2. Inclusion and exclusion criteria. I think you might present here the expected concordance between the 10/66 algorithm and clinical review, based on existing data from the Sub-Saharan African cohorts for example (e.g. the Nigeria data from the original 10/66 study?). It is currently written as if you are blind to what the concordance is going to be but you are presumably fairly confident that these tools will perform well. There is a big resource implication of validating only for the first 25 cases and validating 200. So you might want to suggest some intermediate steps you could take if the first 25 cases suggest a tweak that needs making to the process for this cohort.

Part 2. Procedures. Is the Kyamulibwa Research Station easily accessed by the communities you are working with? Is there a risk of bias introduced here by moving from home-based assessments to those where participants must travel?

Part 2. Procedures. Tobacco smoking is not listed explicitly here, but I assume it is included under 'vascular risk factors'? Perhaps these could be listed in full for clarity. I also wonder if you might include 'poverty' as a potential risk factor to be considered?

Part 2. Procedures. In part 1 you specific that interviewers will be Luganda-speaking. It would be worth re-stating that here (assuming it is the same) and also that you are sure that all participants living in this area have Luganda as their first language.

Part 2. Procedures. There is not a timeline provided in this protocol (perhaps a high-level one would be a useful addition?) but one assumes this work will take several years to complete. The

blood-based biomarker field for neurodegenerative and related biomarkers is rapidly maturing. The current biomarkers available (AB42/40, P-tau, NFL, GFAP) are quite limited in the breadth of pathology they are designed to estimate, when compared to the neuropathologies indicated by autopsy-based studies (see Nichols Lancet Healthy Longevity 2023 https://doi.org/10.1016/S2666-7568(23)00019-3 for example). But it does seem possible that blood tests, perhaps even via finger prick, might be available for a much broader set of biomarkers might be validated and available soon (https://www.alzforum.org/news/conference-coverage/nulisa-new-proteomic-method-revamp-biomarker-analysis). I wonder if you might add a line that you will consider broadening your biomarker panel if further biomarkers are validated (and affordable/implementable) in time.

Part 2. Analysis plan. Again a consideration of the handling of missing data is needed.

Part 3. Procedures. A little more detail could be given here as to what exactly you are trying to elicit from the interviews (currently quite general topics). The advent of scalable biomarkers, the differing diagnostic criteria proposed by the AA Jack et al. group and the IWG and others, all bring back into sharp focus the idea that we don't really have a consensus agreement of what Alzheimer's disease is. And dementia itself means different things in different cultures because what normal cognitive aging is differs across places and time. Cultural beliefs around donation of body tissues and samples can also differ across cultures. It would be good if sufficient space could be given to teasing out some of these foundational questions – 'what does dementia/Alzheimer's/mixed disease, growing old with dignity, brain ageing, mean to you? To your community?'. Before the focus on what services are needed which is obviously also important.

Impact of the study and future work
Tied in with the earlier recommendation to include a paragraph on the study population and the country as a whole. It would be good to include some comment here about how generalisable you think this work is likely to be to the rest of Uganda, and the broader region.

References
1. Nichols E, Merrick R, Hay SI, Himali D, et al.: The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia.*Lancet Healthy Longev*. 2023; **4** (3): e115-e125 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Dementia; public health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jan 2025

Josephine Prynn

Thank you very much for your considered and thoughtful observations and suggestions. We have revised the submission and hope you will agree that it is stronger for the changes.

MAJOR POINTS:

1. Aims and objectives: A major challenge from the public health perspective of seeing the new biomarkers (and the associated agenda of pushes for earlier diagnosis) transition from being research-useful to clinically-meaningful is demonstrating that they change overall outcomes for the better. I can see from your planned methods and data sources that it is not feasible to design a cohort study to empirically investigate this. But I wonder if you might consider this question within your planned qualitative work. A patient has a set of symptoms and functional needs which are elicited clinically. How does providing a diagnosis (a 'precise' one or otherwise) and how does finding out what their pathology status is affect the treatment and subsequent quality of life of that patient? And do these benefits (assuming there are some) outweigh the opportunity costs of the investment and infrastructure required to deliver the biomarkers routinely? What kind of care pathway is likely to produce the greatest patient/economic benefit at scale? These are questions of relevance globally, but perhaps more so in LMICs where the opportunity costs, even of finger prick or blood-based biomarkers, are likely to be more significant.
   Response: Thank you for this observation. We agree that the value in receiving a precise diagnosis is certainly not clear at the moment, although may become so in the future as more effective therapies may become available. The real value of using biomarkers in this study is to gain understanding of the underlying pathological processes leading to dementia, and therefore to understand and promote effective preventative strategies. Furthermore, expanding access to biomarkers aims to help improve equity in diagnostics and drug development so that if or when effective therapy does become available the evidence base comes from diverse populations.

2. Missing data: In the analysis plans of parts 1 and 2 I didn't see any thoughts on how any biases through selection, drop out, incomplete reporting (beyond work with informants) will be mitigated or assessed.
   Response: One of the values of being nested within an established population cohort is that we will have data available describing multiple characteristics of the participants who do not participate, which will help us establish patterns of missingness. Where appropriate, multiple imputation strategies will be used. We have added a statement in the Part 2 analysis plan to describe this.

3. Retinal imaging. This is not explained in much detail. I can see that this may be a

pragmatic alternative to MRI-based assessment of cerebrovascular burden. But perhaps a little more consideration is needed here as to how valid you think retinal imaging is for assessment of cerebrovascular burden (and its spatial distribution through the brain) and associated dementia risk, and to what extent this is really an exploratory (and pragmatic) approach. And in the analysis plan more detail on how you plan to compare the findings of the retinal imaging with the biomarkers. Is it just amyloid pathology and cerebrovascular disease (as measured by retinal imaging) that you plan to include in the PAF calculation? What about the modifiable risk factors? Age?
Response: The analysis plan has been updated to give more detail about the PAF calculation plans.

MINOR POINTS:

Title:
Suggest that you rephrase this for brevity and impact – 'Prevalence, aetiology, and service mapping of dementia in rural Uganda. A case-control study nested in DEPEND (Dementia Epidemiology, unmet Need and co-Developing Solutions) Uganda.'
Response: Updated

Abstract:
Suggest paragraph one, "high" is changed to "higher".
Suggest paragraph four, abbreviations MRC, URI, LSHTM should be spelled out.
Suggest final paragraph you add to the sentence " This paves the way for effective policy strategies for both dementia prevention and support for people with dementia and their families" to include potential for this work to inform research. At the moment you only suggest implications for policy and practice.
Response: All done

Overarching comment:
You use 'prevention' and 'risk reduction' somewhat interchangeably through the manuscript and I wonder if you might go through and select terms more deliberately. Access to antiretrovirals for those with HIV might truly prevent dementia. But addressing the Lancet commission risk factors is likely to have a spectrum of effect and perhaps 'risk reduction' could be more appropriate in this context.
Response: Addressed

Introduction:
In the Dementia Risk Factors section. The sentence: "Together these factors have been estimated to cause around 45% of worldwide dementia cases." I think the current interpretation of the Lancet commission is that 45% of cases are "attributable" (not 'caused by') the combination of these potentially modifiable risk factors.
Response: Done

In the pathological processes leading to dementia section. The sentence: "AD is considered a progressive neurodegenerative condition which is 60–80% heritable, particularly through the APOE4 genetic pathway[15]". You mention some of this later on, but I think you should mention here, that the APOE work (and all genomic dementia work) has been focused

primarily on Caucasian/white European populations, and often in clinical datasets which over-select for younger onset (and therefore presumably higher likelihood of genetic association) cases. Some emerging work has suggested the relationships may be different for different ethnic groups.
Response: Done

This section includes discussion of AD, vascular dementia, and HAND. I think you might add a short additional paragraph after these to mention a) some of the other, rarer causes of dementia (FTD, LBD, reversible forms); and b) that there may be other pathologies which we have not yet fully captured (e.g. recent recognition of the role TDP-43 plays). And other pathological processes, e.g. neuroinflammation, that we haven't fully understood.
Response: Done

Somewhere in the introduction it might be good to include a brief description of Uganda as a place. You reference the provenance of several other pieces of research as being from Northern Uganda or Eastern Uganda. But this might not mean so much to the general reader. Perhaps you could include in this paragraph a very brief note on the demographics of the country as a whole – e.g. what is the life expectancy, median age etc. now, what was it 20, 50 years ago? – OurWorldInData.org is a good source for these kind of data; and also some specific information on the region in focus here (e.g. homogeneity of culture, language spoken, typical occupations, HIV prevalence, typical educational background).
Response: Done

Protocol:
There is mention of stakeholder engagement in part 3 and for dissemination. But I wonder if there is value in initiating this from the outset. Perhaps policymakers and other key stakeholders will have views on what data they need which will add nuance to what data you collect (and how) in parts 1 and 2?
Response: The stakeholder engagement paragraph refers to the whole project, not just Part 3. We have updated the wording to reflect this.

Part 1. Study setting & population. Forgive my ignorance, but are there any social care facilities or similar entities in this part of Uganda where people would reside if there were perceived challenges to them living well at home? As the authors will know, in HICs a key part of dementia epidemiology is a sampling strategy that includes those not residing in the community, but in health or social care facilities. It may well be that this is irrelevant in this region.
Response: We have now this in the first paragraph of Part 1.

Part 1. Population. "We aim to recruit all of those with impaired cognition at screening (defined as ≤1.5 SDs below the mean), a random sample of 50% of those with mildly impaired cognition (≤1 to <1.5 SD below the mean), and a random sample of 15% of those with unimpaired cognition (>1 SD below the mean)". I think all of the greater than/less than signs here are the wrong way round? Please sense check.
Response: This depends on whether the "less than" signs refer to the score or the standard deviation! Impaired cognition is indicated by a score that is lower than 1.5 SDs below the mean. Therefore a score that is at least 1.5 SDs below the mean (i.e. more than 1.5 SDs).I've

changed the language to make it less ambiguous.

Part 1. Analysis plan. I wonder if you might consider analysing whether the sensitivity and specificity of the screening tools differ by participant characteristic. For example, by stratifying the analysis by sex, by years of education (via a binary cut off), by cognitive score, by age, and/or by language spoken or ethnocultural group (if there is heterogeneity in the region). **Response:** Thank you for the suggestion. We are concerned that the stratified analysis would be underpowered, but will assess for bias using a logistic regression modelling approach which we have now outlined in the paper.

Part 1. Analysis plan. Please comment on what you plan to do about missing data (e.g. from those not able to complete the 50-90 minute appointment).
Response: We have included additional information about the GMS which captures interviewer observation data which helps explain missing data and allows identification of dementia even with an incomplete assessment.

Part 2. Inclusion and exclusion criteria. I think you might present here the expected concordance between the 10/66 algorithm and clinical review, based on existing data from the Sub-Saharan African cohorts for example (e.g. the Nigeria data from the original 10/66 study?). It is currently written as if you are blind to what the concordance is going to be but you are presumably fairly confident that these tools will perform well. There is a big resource implication of validating only for the first 25 cases and validating 200. So you might want to suggest some intermediate steps you could take if the first 25 cases suggest a tweak that needs making to the process for this cohort.
Response: This is a helpful suggestion – we have added a step in which we would attempt to adjust the diagnostic process if concordance is low.

Part 2. Procedures. Is the Kyamulibwa Research Station easily accessed by the communities you are working with? Is there a risk of bias introduced here by moving from home-based assessments to those where participants must travel?
Response: We have clarified in the text that we will provide transport for those unable to travel independently.

Part 2. Procedures. Tobacco smoking is not listed explicitly here, but I assume it is included under ‘vascular risk factors’? Perhaps these could be listed in full for clarity. I also wonder if you might include ‘poverty’ as a potential risk factor to be considered?
Response: We are assessing for poverty and early life adversity, which I have added to the list, and have clarified which vascular risk factors we are able to assess.

Part 2. Procedures. In part 1 you specific that interviewers will be Luganda-speaking. It would be worth re-stating that here (assuming it is the same) and also that you are sure that all participants living in this area have Luganda as their first language.
Response: Done

Part 2. Procedures. There is not a timeline provided in this protocol (perhaps a high-level one would be a useful addition?) but one assumes this work will take several years to complete. The blood-based biomarker field for neurodegenerative and related biomarkers

is rapidly maturing. The current biomarkers available (AB42/40, P-tau, NFL, GFAP) are quite limited in the breadth of pathology they are designed to estimate, when compared to the neuropathologies indicated by autopsy-based studies (see Nichols Lancet Healthy Longevity 2023 https://doi.org/10.1016/S2666-7568(23)00019-3 for example). But it does seem possible that blood tests, perhaps even via finger prick, might be available for a much broader set of biomarkers might be validated and available soon (https://www.alzforum.org/news/conference-coverage/nulisa-new-proteomic-method-revamp-biomarker-analysis). I wonder if you might add a line that you will consider broadening your biomarker panel if further biomarkers are validated (and affordable/implementable) in time.
Response: Done.

Part 2. Analysis plan. Again a consideration of the handling of missing data is needed.
Response: Done.

Part 3. Procedures. A little more detail could be given here as to what exactly you are trying to elicit from the interviews (currently quite general topics). The advent of scalable biomarkers, the differing diagnostic criteria proposed by the AA Jack et al. group and the IWG and others, all bring back into sharp focus the idea that we don't really have a consensus agreement of what Alzheimer's disease is. And dementia itself means different things in different cultures because what normal cognitive aging is differs across places and time. Cultural beliefs around donation of body tissues and samples can also differ across cultures. It would be good if sufficient space could be given to teasing out some of these foundational questions – 'what does dementia/Alzheimer's/mixed disease, growing old with dignity, brain ageing, mean to you? To your community?'. Before the focus on what services are needed which is obviously also important.
Response: We agree that exploring the cultural conceptualisation of ageing, brain health and dementia is very important when considering the experiences of people living with dementia and the services available for them, and will be included within the interviews. We have added this more clearly in the text.

Impact of the study and future work
Tied in with the earlier recommendation to include a paragraph on the study population and the country as a whole. It would be good to include some comment here about how generalisable you think this work is likely to be to the rest of Uganda, and the broader region. **Response:** The text has been updated.

Competing Interests: No competing interests were disclosed.