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Predictors of White Matter Hyperintensities (WMH) in the elderly Congolese population

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Master of Public Health

Applied Epidemiology

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Medical Doctor (MD)

University of Kinshasa

2010

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Abstract

Predictors of White Matter Hyperintensities (WMH) in the elderly Congolese population

By Emile Omba Yohe

Objectives: White matter disease is a general term for changes and damage to the brain's white matter, which can be seen as a bright spot on magnetic resonance imaging (MRI) of the brain, called white matter hyperintensities (WMH). WMHs are strongly linked to cardiovascular risk factors and other health conditions like Alzheimer's disease in high-income countries and populations of European ancestry. However, there is no evidence of these associations in the Congolese population. This study evaluates factors associated with WMH in the elderly Congolese population.

Methods: In a cross-sectional study of 77 people from the Democratic Republic of Congo (DRC), participants were categorized as having dementia or being a healthy control group based on their cognitive tests. Then, participants' brain MRIs were performed to analyze their WMH volume. A simple linear regression model was conducted to test the association between WMH and each considered predictor (neurological status, age, sex, hypertension, diabetes, tobacco abuse, stroke, high cholesterol, cardiovascular medication, and alcohol abuse). Then, stepwise selection and backward elimination were performed to obtain the final model. Finally, a multiple linear regression model was conducted to assess the association of WMH and variables retained in the final model (neurological status, sex, and age).

Results: Of the 77 sample population, 47 (61%) had dementia, 40 (52.6%) were males, and the mean age was 73 years (± 8.0 years standard deviation). In simple linear regression models, WMH was significantly associated with dementia ($\exp\beta 1$ =1.75, 95% CI =1.14 – 2.71, p-value =0.01) and had a weak association with age ($\exp\beta 1$ =1.03, 95% CI =1.00 – 1.05, p-value =0.05) and sex (male) ($\exp\beta 1$ =0.66, 95% CI =0.43 – 1.01, p-value =0.05). In multiple linear regression models, WMH was statistically significantly associated with dementia ($\exp\beta 1$ =1.97, 95% CI =1.31 – 2.95, p-value =0.001), sex (male) ($\exp\beta 2$ =0.54, 95% CI =0.36 – 0.80, p-value =0.003), and age ($\exp\beta 3$ =1.03, 95% CI =1.00 – 1.06, p-value =0.03). However, WMH was not significantly associated with common cardiovascular risk factors, such as high blood pressure, diabetes, tobacco use, obesity, and high cholesterol levels.

Conclusion: WMH is significantly associated with neurological status, sex, and age in the Congolese population. Understanding these predictors of WMH may be a helpful prevention tool for white matter disease in Sub-Saharan African countries, especially in DRC, where brain MRI diagnosis is difficult to obtain.

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Background

White matter disease

White matter comprises an extensive network of nerve fibers (axons) in the human brain that allows the exchange of information and communication between different brain areas. The name "white matter" was given to these nerve fibers due to their covering in a protective sheath called myelin, which gives the tissue its white color [1].

White matter disease is an umbrella term for changes and damage to the brain's white matter. When white matter becomes damaged, it causes white matter lesions, which can be seen as bright spots on magnetic resonance imaging (MRI) of the brain, called white matter hyperintensities (WMH) [1].

WMHs represent a challenging situation in studying the brain's health and disease. The prevalence of WMH is estimated to be between 20% and 50% in the general population in midlife, increasing to more than 90% with advanced age [2,3]. WMHs as revealed by an MRI of the brain are a marker of change to the brain's connective nerve fibers, potentially contributing to cognitive decline, balance, and mobility issues [1, 2]. Signs and symptoms of white matter disease include memory problems, mobility disturbance (e.g., particularly slow movements), balance issues (falls), difficulty performing two or more activities at once (e.g., walking and talking at the same time), mood changes (e.g., depression), and urinary incontinence [1]. These signs and symptoms can be associated with normal aging changes and other medical conditions. WMHs are strongly linked to cardiovascular disease risk factors, and evidence shows that WMHs are a biomarker of the lifelong risk of stroke, dementia, and disability [1]. Moreover,

larger WMH volume has been associated with Alzheimer's disease (AD) and cognitive decline [4].

White matter disease and Dementia

Dementia, one of the top five causes of death globally, describes the state of a person's mental function and not a specific disease. It is an umbrella category representing cognitive decline severe enough to interfere with daily living and characterized by difficulties with memory, language, problem-solving, and other thinking skills [5, 6, and 7]. Dementia develops when the parts of the brain involved with learning, memory, decision-making, or language are affected by infections, degenerative diseases, or other neurological diseases or injury [7].

There are many underlying causes of dementia, with AD being the most common [7]. AD, the leading cause of dementia in individuals aged 65 or older, is a significant global burden, with 40-50 million people currently living with AD-related dementia and predicted to be over 150 million by 2050 [5, 8, and 9]. AD is characterized by complex brain changes, which may begin a decade or more before symptoms appear. During the early stage of AD, there is an abnormal buildup of proteins that form amyloid plaques and tau tangles, making healthy neurons stop functioning and die [10]. The damage initially appears in the hippocampus and entorhinal cortex, which are parts of the brain essential to forming memories. As more neurons die, additional brain regions are affected and appear atrophied on MRI or post-mortem exam. By the final stage of AD, the damage is widespread, and brain tissue has become significantly atrophied [10]. In AD, the observed patterns of WMH can reflect the advanced phase of the disease as evidence shows significant and anatomically congruent correlations between WMH and regional gray matter atrophy in patients with AD [11]. Parietal WMH is a substantial predictor of cortical AD

pathology. Therefore, AD should also be considered the leading underlying cause of dementia in cases with parietal WMH [12]. WMHs are found in more than 89% of patients with AD and are typically more severe than WMHs seen in older people without dementia [12].

Other known causes of dementia include vascular dementia, dementia with Lewy bodies, fronto-temporal dementia, and dementia due to Parkinson's disease [7].

White matter disease and Cardiovascular risks and disease

Currently, cardiovascular disease (CVD) is the leading cause of premature mortality and morbidity worldwide, with 80 % of cases coming from lower-income countries [13]. The Centers for Disease Control and Prevention (CDC) states that heart disease is the primary cause of death in the United States, leading to about 695,000 deaths in 2021 [14]. Heart disease is the main cause of healthcare expenditure in the USA, including the cost of healthcare services, medicines, and lost productivity due to deaths; from 2018 to 2019, heart disease cost the USA about $ 239.9 billion [14].

Research on CVD shows that it is associated with many risk factors. The major CVD risk factors include smoking, hypertension, diabetes, dyslipidemia, physical inactivity, being overweight, and obesity [13, 14].

Vascular dementia is the second most common type of dementia, caused by conditions that block and damage blood vessels in the brain. About 25 % of persons with dementia have vascular dementia, and associated risk factors include high blood pressure, diabetes, and high cholesterol levels [7].

In older adult populations, WMHs are primarily considered a consequence of cerebral small-vessel disease (cSVD). Evidence shows a significant positive association between the extent of atherosclerotic cardiovascular disease and WMH volume [2]. Also, researchers have found associations between cardiovascular risk factors, WMH burden, and time to event for stroke and cognitive impairment [2]. Furthermore, the authors find cardiovascular risk factors, such as hypertension, have direct and indirect associations with WMH [2]. In the Rotterdam Scan Study, researchers found that increased arterial stiffness is associated with a larger volume of WMH in patients with uncontrolled hypertension [15]. Due to arterial stiffness, high blood pressure causes gradual damage to small-vessel beds and dysfunction of brain barriers, leading to cSVD [2, 15].

White matter disease and Age and Sex

The prevalence of white matter disease increases with age, as it is less than 50% in midlife but more than 90% in older adults [2]. Midlife WMH tends to grow and proliferate from existing lesions, leading to a faster cognitive decline at a later age [16]. Researchers have demonstrated that the association between WMHs and early signs of cognitive decline is detectable many years before the emergence of clinical symptoms of Alzheimer's disease and related dementia (ADRD); therefore, WMHs can be measured in the brains of older adults as a surrogate biomarker of cognitive decline and risk of dementia [16].

The prevalence of WMHs is associated with the female sex, as research shows that women usually have more severe cerebral white matter lesions than men, leading to a higher incidence and prevalence of dementia in women than in men in older adults [17].

White matter disease in the Democratic Republic of Congo

The African population is aging at a higher rate, making age-related diseases like dementia a significant public health issue. Given that WMH risk increases with age, it is crucial to focus on the African population [18]. The African countries are undergoing the third phase of the epidemiological transition, characterized by a shift in the overall burden of morbidity and mortality from infectious diseases to non-communicable diseases and injuries [19]. Due to an increase in life expectancy, the worldwide population is aging, with an increased number of people aged 60 years and over. However, the demographic change is occurring faster in low and middle-income countries (LMIC) than it was during the last century in high-income countries (HIC) [20].

Consequently, the most considerable proportion of the predicted increase in dementia-related diseases like WMHs will occur in LMIC, especially in East Asia and Sub-Saharan Africa (SSA), where more than 70% of people with dementia are expected to live in 2040 [19,20]. In an Epidemiologic study conducted in central Africa, researchers found that patients with dementia had 2.5 times higher mortality risk than participants with normal cognition (HR=2.53, 95 % CI= 1.42-4.49, P= 0.001) [19]. Given the predicted increase in prevalence of WMH in LMIC, such as the D.R. Congo, and the lack of literature on the burden of WMH on the Congolese population, further research in D.R. Congo is needed to understand factors associated with WMH, which will help to improve population health outcomes.

Rational for Thesis

Substantial research has been conducted to prove the association between cardiovascular risk factors, AD, and WMH. However, most of this research has been conducted in HIC and

populations of European ancestry. Few studies on WMH have been carried out in sub-Saharan Africa, and none specifically in the D.R. Congo. When considering the Congolese populations, public health authorities may not directly apply research conducted in HIC and populations of European ancestry because the prevalence of WMH and the distribution of WMH-associated risk factors may be different from HIC populations.

Given that the African population is aging at a high rate, and there is an increase in non-communicable diseases (cardiovascular diseases, diabetes, obesity) and dementia, it is critical to focus our research on determining conditions and risk factors associated with white matter change in the African populations.

WMHs are the tip of the iceberg of multiple pathologic features useful to predict brain health models. As WMHs are slowly progressive, early detection will provide the opportunity for early intervention to reduce risk, prevent disease progression, and avoid cognitive impairment and stroke.

Based on past research on WMH in high-income countries and populations of European ancestry, we hypothesized that WMH would be significantly associated with cardiovascular-related risk factors (hypertension, diabetes, high blood cholesterol, obesity, and smoking) and Alzheimer's disease-related dementia in the elderly Congolese population.

Methods

1. Study design and population

This cross-sectional study was conducted from 2019 to 2022 in Kinshasa, the Democratic Republic of Congo (DRC). Initially, 1432 people were selected through a

community-based recruitment procedure from door-to-door in the city, clinics, hospitals, churches, and older adult associations. Then, selected participants were screened for dementia using the Community Screening Instruments for Dementia (CSID) and Alzheimer's Questionnaire (AQ) measures. Written informed consent was obtained from all participants before undergoing any study procedures approved by the Ethical Committee and Institutional Review Boards of the University of Kinshasa. All participants were financially compensated for their time [21].

- ***Inclusion criteria***

People included in this study were those who were 50 years or older, met the criteria of major neurocognitive disorder or normal cognition according to DSM-5, had close contact to serve as a collateral informant, were able to give informed consent, were fluent in French or Lingala, and had adequate sensory-perceptual skills to be able to see and draw for cognitive tests.

- ***Exclusion criteria***

Participants were excluded from this study if they had a subjective memory complaint, mild neurocognitive disorder, history of schizophrenia, neurological, or other medical conditions potentially affecting the central nervous system (CNS).

2. *Measurement of cognitive ability*

Due to the lack of clear cutoff values for AD biomarkers in the SSA to clinically confirm the diagnosis of probable AD, we used screening measures to diagnose major neurocognition disorder or possible dementia (pD). Participants were administered the CSID and AQ test to screen for dementia. First, participants were classified into two different groups based on their CSID scores: cognitively impaired (CSID score of < 25.5) or cognitively unimpaired (CSID

score of ≥ 25.5). Next, participants were classified within each group of the CSID score test based on the AQ scores: cognitively impaired (AQ score of > 13) or cognitively unimpaired (AQ score of ≤ 13). Finally, participants were classified based on the two cognitive tests in four different sub-groups, which were **major neurocognitive disorders** (CSID < 25.5 and AQ > 13), **mild neurocognitive disorders** (CSID < 25.5 and AQ ≤ 13), **subjective neurocognitive impairment** (CSID ≥ 25.5 and AQ > 13), and **normal cognition** (CSID ≥ 25.5 and AQ ≤ 13) [21].

For this study, only participants in the major neurocognitive disorder group, considered to have dementia, and the individuals in the normal cognition group, considered healthy controls, were included in the analysis. Of 1432 initially recruited participants, only 271 met the above criteria for major neurocognitive disorders or normal cognition. Among participants who met the criteria, 88 individuals had major neurocognitive disorder, and 183 were considered healthy subjects with normal cognition. Healthy controls (HC) were matched based on age, sex, and education levels before the MRI procedure.

After this classification, an expert panel of neurologists, psychiatrists, and neuropsychologists assessed the participants, and they confirmed 61 individuals with a diagnosis of major neurocognitive disorders or possible dementia (pD) and 54 individuals as healthy controls (HC). For this study, participants with neurocognitive disorders are considered as having dementia and will not be identified as individuals with possible AD.

Neuroimaging (Brain MRI) was then performed, resulting in the final sample of 77 subjects with 47 pD and 30 HC. Some of the remaining 46 subjects did not have their Brain MRI due to limited funds, and others were excluded because their neuroimaging evidence indicated an etiology other than probable AD (e.g., presence of a brain tumor) [Figure 1].

3. Descriptive Measurements

The demographic, socioeconomic, and medical history information was obtained through participants' self-reported questionnaires and interviews. Based on their ages, participants were categorized into four different age groups: 50-64, 65-74, 75-84, and 85+. Based on their education levels, individuals were classified into four different groups: primary school (1-6 years), secondary school (7-12 years), some or completion of university (13-17 years), and beyond university (18+ years).

After three blood pressure measurements by a medical resident at complete rest, a participant was considered to have hypertension if their systolic blood pressure was greater than 139 mmHg and diastolic blood pressure greater than 89 mmHg.

A participant was considered to have diabetes mellitus type 2 if their blood sugar had an HbA1C level $\geq$ 6.5 % or having a fasting blood glucose $\geq$ 7.0 mmol/l.

4. *Neuroimaging Parameters*

Each participant was scanned using a 1.5 Tesla MRI unit scanner (Siemens, Magneton Sonata) at HJ Hospitals in Kinshasa, DRC, using the same standardized imaging acquisition protocol based on the Alzheimer's Disease Research Center (ADRC) protocol of Emory University [22]. It consisted of sagittal volumetric T1-weighted (MP-RAGE), coronal T2-weighted, axial diffusion-weighted, T2-weighted, and T2-FLAIRE sequences. High-resolution structural images were obtained using a T1-weighted MP-RAGE Sequence with the following parameters: Repetition Time (TR) = 2200 ms; minimum full Echo time (TE) = 1000 ms; Flip

angle = 8^0; Field of view (FOV) = 250 mm; acquisition matrix= 192 X 184, yielding a voxel size of approximately 1.25 mm X 1.25mm X 1.2 mm.

5. *Quantification of WMHs*

To identify and extract WMH volume, brain segmentation was performed by experts at Emory University. An experienced subspecialty-certified neuroradiologist reviewed images to ensure that automated processes resulted in reasonable data. White matter hyperintensity was graded according to the age-related white matter changes (ARWMC) scales [22]. The number of chronic brain parenchymal micro hemorrhages was recorded, and the lobar volume loss pattern of the brain was assessed. Regional brain volume for both cortical and sub-cortical brain regions was calculated. Finally, the presence or absence of any additional abnormalities was noted, and participants with neuroimaging evidence indicated an etiology other than probable AD (e.g., the presence of a brain tumor) were excluded from the analysis.

The Fazekas scale for white matter lesions was used to quantify the amount of white matter T2 hyperintense lesions [22]. The Fazekas scale is mainly used to describe white matter disease severity, and it divides the white matter into periventricular and deep white matter. Each region is graded based on the size and confluence of lesions. For this analysis, we used the deep white matter (DWM) classification:

- 0 = absent
- 1 = punctate foci
- 2 = beginning confluence
- 3 = large confluence areas.

The deep white matter score is crucial in assessing patients with possible dementia, and it is the component that is usually reported (e.g., Fazekas grade 2) [22].

Statistical Analysis

All statistical analyses were completed using SAS version 9.4 statistical software. First, descriptive statistics (e.g., frequencies, percentages, means, and standard errors) were generated for the sample as a whole and the two groups of differing neurological status (Table 1). Second, WMH volume was log-transformed for normality. Third, a univariable analysis in a simple linear regression model was conducted to test the association between WMH (dependent variable) and each predictor (primary independent variable). The predictors that we considered were neurological status, age, age decade, sex, hypertension, diabetes, tobacco abuse, stroke, high cholesterol, cardiovascular medication, and alcohol abuse. Finally, a multivariable analysis in a multiple linear regression model was conducted to assess the association of WMH and all the predictors retained in the final model. Multivariable analysis started with a stepwise selection using a p-value cut-off of 0.20 for variable entry and removal. Then, backward elimination was performed to remove insignificant variables at the 0.05 level to obtain the final model. The predictors that were retained in the final model were neurological status, sex, and age. The final model helped to analyze the relationship between WMH and its predictors when controlling for other confounders. The results were expressed as exp (beta) coefficients with corresponding 95% confidence intervals. All statistical tests were two-sided; p-values < 0.05 were considered statistically significant.

RESULTS

Descriptive characteristics of the sample population

Of 1432 baseline participants enrolled in this study, 77 had brain imaging (MRI) data and were included in the analysis; their demographics and medical history were reported in Table 1. Overall, the sample population consisted of 47 dementia cases and 30 healthy controls, and participants were evenly distributed between males (52.6%) and females (47.4%). The mean age was 73 years in the population, while participants' age groups, education levels, and body mass index were similar between dementia and control groups, showing that matching was performed appropriately.

Regarding medical history, the sample mean WMH volume was 13,151 mm^3, with dementia cases having a higher mean WMH volume (15,745 mm^3) than healthy controls (9,088 mm^3). A little more than half of the participants (51.3%) had hypertension, with a higher prevalence among dementia compared to the control cases (55.3% and 44.8%, respectively). Additionally, more dementia cases (11%) reported a history of stroke compared to the healthy control cases (0%).

Association between WMH and its predictors

The association between WMH and its predictors was performed using the log-transformed value of WMH volume (Figure 2) in simple and multiple linear regression models.

- ***Univariable Analysis: Association between WMH and each predictor***

In a simple linear regression model, WMH was significantly associated with neurological status (Dementia) ($\exp\beta_1$ =1.75, 95% CI =1.14 – 2.71, p-value =0.01). Participants with Dementia had a 75% increase in WMH volume compared to healthy controls. WMH had a

statistically weak association with age ($exp\beta_1$ =1.03, 95% CI =1.00 – 1.05, p-value =0.05) and sex (male) ($exp\beta_1$ =0.66, 95% CI =0.43 – 1.01, p-value =0.05). Male participants had a WMH volume 34% lower than Female participants, and when participants' age increases by 1 year, it is associated with a 3% increase in WMH volume. There were no statistically significant associations between WMH and other predictors, such as age decade ($exp\beta_1$ =1.21, 95% CI =0.94 – 1.56, p-value =0.12), diabetes ($exp\beta_1$ =1.84, 95% CI =0.82 – 4.10, p-value =0.13), alcohol abuse ($exp\beta_1$ =0.67, 95% CI =0.38 – 1.16, p-value =0.15), tobacco abuse ($exp\beta_1$ =1.66, 95% CI =0.78 – 3.50, p-value =0.18), stroke ($exp\beta_1$ =0.72, 95% CI =0.32 – 1.58, p-value =0.40), high cholesterol ($exp\beta_1$ =1.42, 95% CI =0.53 – 3.79, p-value =0.48), hypertension ($exp\beta_1$ =0.85, 95% CI =0.56 – 1.35, p-value =0.54), and cardiovascular medication ($exp\beta_1$ =0.93, 95% CI =0.52 – 1.67, p-value =0.81) [Table 2].

- ***Multivariable Analysis: Association between WMH and all the variables from the final model***

The summary of the stepwise selection process showed that four variables were selected: neurological status ($exp\beta_1$ =1.95, 95% CI =1.30 – 2.93, p-value = 0.001), sex (Male) ($exp\beta_2$ =0.53, 95% CI =0.36 – 0.80, p-value =0.003), age ($exp\beta_3$ =1.03, 95% CI =1.00 – 1.05, p-value =0.03), and tobacco abuse ($exp\beta_4$ =1.59, 95% CI =0.81 – 3.12, p-value =0.17) [Table 3].

Then, after the backward elimination process, only three variables were retained in our final model: neurological status ($exp\beta_1$ =1.97, 95% CI =1.31 – 2.95, p-value =0.001), sex (Male) ($exp\beta_2$ =0.54, 95% CI =0.36 – 0.80, p-value =0.003), and age ($exp\beta_3$ =1.03, 95% CI =1.00 – 1.06, p-value =0.03) [Table 4].

The multivariable analysis showed a statistically significant association between WMH and all three variables in the final model. Neurological status (Dementia) was significantly associated with WMH when controlling sex and age. Participants with dementia had two times higher (97% increase) volume of WMH than the healthy controls, controlling for sex and age. Sex (Male) was significantly less associated with WMH, adjusted for neurological status and age. Male participants had a 46% decrease in WMH volume compared to females, controlling for neurological status and age. Age was significantly associated with WMH, controlling neurological status and sex. The increase in 1 year of age was associated with a 3% increase in participants' WMH volume, controlling for neurological status and sex [Table 4].

DISCUSSION

Major Findings

We explored the association between WMH and its predictors in a community-based sample from Kinshasa, the DRC. For the unadjusted analysis, we found a significant association between WMH and neurological status and a weak association between WMH and the sex and age of the participants. In the adjusted analysis, dementia status, older age, and female sex were significantly associated with a larger volume of WMH independently of each other.

Biological Plausibility

Our findings underscore a significant association between WMH and dementia, which may have different origins, such as vascular or Alzheimer's disease. Alterations to cellular and physiological components of the brain are linked to white matter health and the burden of WMH.

The neuro-glio-vascular unit, composed of neurons, astrocytes, microglia, oligodendrocytes, and vascular cells, regulates cerebral blood flow and brain function. Damage to any component of the neuro-glio-vascular unit can lead to WMH and cognitive impairment [2].

In vascular dementia, WMH burden is associated with neurovascular inflammation, which is a key mechanism in the etiology of WMH [23]. Vascular inflammation associated with cardiovascular risk factors and diseases, like hypertension, diabetes, and high blood cholesterol levels, leads to a decrease in cerebral blood flow due to gradual damage to cerebral small vessel beds and dysfunction of brain barriers [2,23]. Cerebral small vessel disease is the major vascular cause of dementia and is a critical risk factor for the transformation of normal-appearing white matter to WMH [23].

In AD-related dementia, WMH is linked to an increased cerebral amyloid angiopathy and parietal Tau burden. The formation of amyloid plaques and Tau tangles in AD will damage healthy neurons and make them die [10]. In the advanced AD state, more brain cells have atrophied and died, which will lead to an increase in WMH volume and dementia [10, 11].

Previous Literature

Previous research suggests that WMH is associated with an increased risk of cognitive dysfunction and is found in most patients with AD-related dementia [12, 24]. Additionally, researchers suggest that white matter diseases start at midlife, and their prevalence increases as people get older, with more than 90% of WMH cases seen in older adults [2]. Moreover, previous studies showed an association between WMH and sex, as the female population had a higher incidence and prevalence of white matter diseases than the male population [17]. These results align with our findings since WMHs were significantly associated with neurological

status (dementia), sex, and age of participants. Our results were meaningfully similar to published studies of populations in HIC.

Public Health Implication

This study outlines factors associated with WMH in the elderly Congolese population. We identified an association between WMH and three main predictors: neurological status (Dementia), sex, and age. Our findings provide essential preliminary data to build better intervention and prevention programs or improve existing programs. For example, our study found a significant association between WMH and dementia. Previous studies found an association between cardiovascular risk factors, WMH, and cognitive impairment [2], so our findings will be critical for preventing dementia in SSA countries like the DRC. Based on our findings in the DRC, the implementation of public health intervention, such as prevention of high blood pressure, diabetes, and obesity, promotion of physical exercise, and decrease in the consumption of tobacco in the population will help to decrease the incidence and prevalence of CVD, which is critical in the occurrence and progression of WMH and dementia. However, we didn't find associations between CVD risk factors and WMH. Additionally, our findings can be used as a starting point to advocate for strong public health laws in the DRC to stop the promotion and limit the use of tobacco and tobacco-related products, the number one cardiovascular risk factor. Public health programs that target individual behavioral change to prevent WMH and stop white matter diseases from getting worse will be relevant in decreasing the burden of dementia (disability and loss of life, social isolation, discrimination, stigmatization, and death) in the Congolese population.

Strengths and Limitations

This study had many strengths related to the study design, setting, and statistical analysis methods. First, the DRC is an understudied place for AD-related dementia. Therefore, this research adds to existing knowledge of white matter disease and its associated predictors in the Congolese population. Second, researchers were familiar with the geographic area and the population of interest, which enhanced partnership and communication. Third, participants were examined by an expert panel to confirm their cognitive ability to avoid any misclassification. Fourth, participants were matched on age, sex, and education levels based on their neurological status (dementia or healthy control groups). Lastly, WMH quantification was performed by experts, and images were reviewed by an experienced neuroradiologist for data accuracy.

This study, like many others, has some limitations. First, the population under investigation in Sub-Saharan, like in the DRC, lacks variability in race and ethnicity, making this study less generalizable to other populations. Second, our study was limited by a relatively small sample size (77 participants), reducing our power to detect the association between WMH and cardiovascular risk factors, such as high blood pressure, diabetes, tobacco use, alcohol use, and high blood cholesterol. Lastly, cross-sectional data provide information from a single point in time, limiting the ability to draw valid conclusions regarding the temporal relationships between WMH and its predictors.

CONCLUSION

White matter disease is common in the general population. They can be caused by numerous factors, such as cardiovascular risks and disease, AD-related dementia, age, and sex.

Understanding the association between WMH and its predictors is crucial in implementing early diagnosis, prevention programs, and treatment. This study found that WMH is significantly associated with neurological status (dementia), sex (females), and age (older adults) in the Congolese population. Knowing these predictors of WMH in the Congolese population could be a useful prevention tool for white matter disease in SSA countries, especially in DRC, where brain MRI diagnosis is difficult to obtain. As this is the first WMH-related study to be done in DRC, more studies with larger sample sizes are needed in which the association between WMH and its predictors is examined from the same population for better comparison and further validation of other predictors that were not significantly associated with WMH in our study, like cardiovascular risk factors (high blood pressure, tobacco use, diabetes, high blood cholesterol, and obesity).

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TABLES AND FIGURES

Table 1: Descriptive Characteristics of the sample population, stratified by Neurological Status

Variables, n (%) or mean (SD)	Health Controls(n=30)	Dementia cases (n=47)	Overall (n=77)
Demographics			
Male	18 (62.1%)	22 (46.8%)	40 (52.6%)
Body Mass Index, kg/m^2*	19.4 (9.9)	20.7 (9.04)	20.2 (9.4)
Age, years	71.6 (8.6)	73.04 (7.7)	72.5 (8.04)
Age groups, years†			
50-64	3 (10.3%)	4 (8.5%)	7 (9.2%)
65-74	9 (31%)	11 (23.4%)	20 (26.3%)
75-84	13 (44.8%)	23 (48.9%)	36 (47.4%)
85+	4 (13.8%)	9 (19.2%)	13 (17.1%)
Years of education*	10.7 (5.2)	8.2 (5.3)	9.13 (5.4)
Education levels, Years†			
Primary school (1-6)	1 (3.5%)	6 (12.8%)	7 (9.2%)
Secondary School (7-12)	5 (17.2%)	14 (29.8%)	19 (25%)
Some/Completed University (13-17)	13 (44.8%)	17 (36.2%)	30 (39.5%)
Beyond University (18+)	10 (34.5%)	10 (21.3%)	20 (26.3%)
Medical History			
WMH volume, mm^3*	9087 (9830)	15744 (15467)	13151 (13869)
WMH-Fazekas†			
Absent	5 (18.5%)	0 (0.00%)	5 (6.8%)
Punctuate foci	13 (48.2%)	25 (54.4%)	38 (52.1%)
Beginning confluence	8 (29.6%)	9 (19.6%)	17 (23.3%)
large confluence areas	1 (3.7%)	12 (26.1%)	13 (17.8%)
Hypertension	13 (44.8%)	26 (55.3%)	39 (51.3%)
Diabetes	5 (17.2%)	1 (2.1%)	6 (7.8%)
High cholesterol	3 (10.3%)	1 (2.1%)	4 (5.3%)
Stroke	0 (0.0%)	5 (10.6%)	5 (6.6%)
Tobacco abuse	3 (10.3%)	4 (8.5%)	7 (9.21%)
Alcohol abuse	4 (13.8%)	10 (21.3%)	14 (18.4%)
Cardiovascular medication	7 (24.1%)	6 (12.8%)	13 (17.1%)

WMH: While Matter Hyperintensity
* These variables are reported as mean (SD)
† These values may not sum to the total due to missing data

Table 2: Univariable Analysis: Association between WMH and each predictor

Variable	Exp(β)	95%CI	p-value
Neurological status	1.75	1.14-2.71	0.01
Age, per year	1.03	1.00-1.05	0.05
Age decade	1.21	0.94-1.56	0.14
Sex (Male)	0.66	0.43-1.01	0.05
Hypertension	0.87	0.56-1.35	0.54
Diabetes	1.84	0.82-4.10	0.13
Tobacco abuse	1.66	0.78-3.5	0.18
Stroke	0.72	0.32-1.58	0.4
High Cholesterol	1.42	0.53-3.79	0.48
Cardiovascular medication	0.93	0.52-1.67	0.81
Alcohol abuse	0.67	0.38-1.16	0.15

WMH: While Matter Hyperintensity.
Our results are presented as the exponentiated beta value of each predictor considered in a simple linear regression model. The result corresponds to the relative increase or decrease in WMH volume associated with a specific variable.

Table 3: Summary of stepwise selection

Variable	Exp(β)	95%CI	p-value
Neurological status	1.95	1.30-2.93	0.001
Sex (Male)	0.53	0.36-0.80	0.003
Age, per year	1.03	1.00-1.05	0.03
Tobacco abuse	1.59	0.81-3.12	0.17

stepwise selection using a p-value cut-off of 0.20 for variable entry and removal. Our results are presented as the exponentiated beta value of each predictor considered in a multiple linear regression model. The result corresponds to the relative increase or decrease in WMH volume associated with a specific variable.

Table 4: Summary of backward elimination/ Final model

Variable	Exp(β)	95%CI	p-value
Neurological status	1.97	1.31-2.95	0.001
Sex (Male)	0.54	0.36-0.80	0.003
Age, per year	1.03	1.00-1.06	0.03

backward elimination was performed to remove insignificant variables at the 0.05 level to obtain the final model. Our results are presented as the exponentiated beta value of each predictor considered in the final model of a multiple linear regression model. The result corresponds to the relative increase or decrease in WMH volume associated with a specific variable.

Figure 1: Flow Diagram of Participant Recruitment

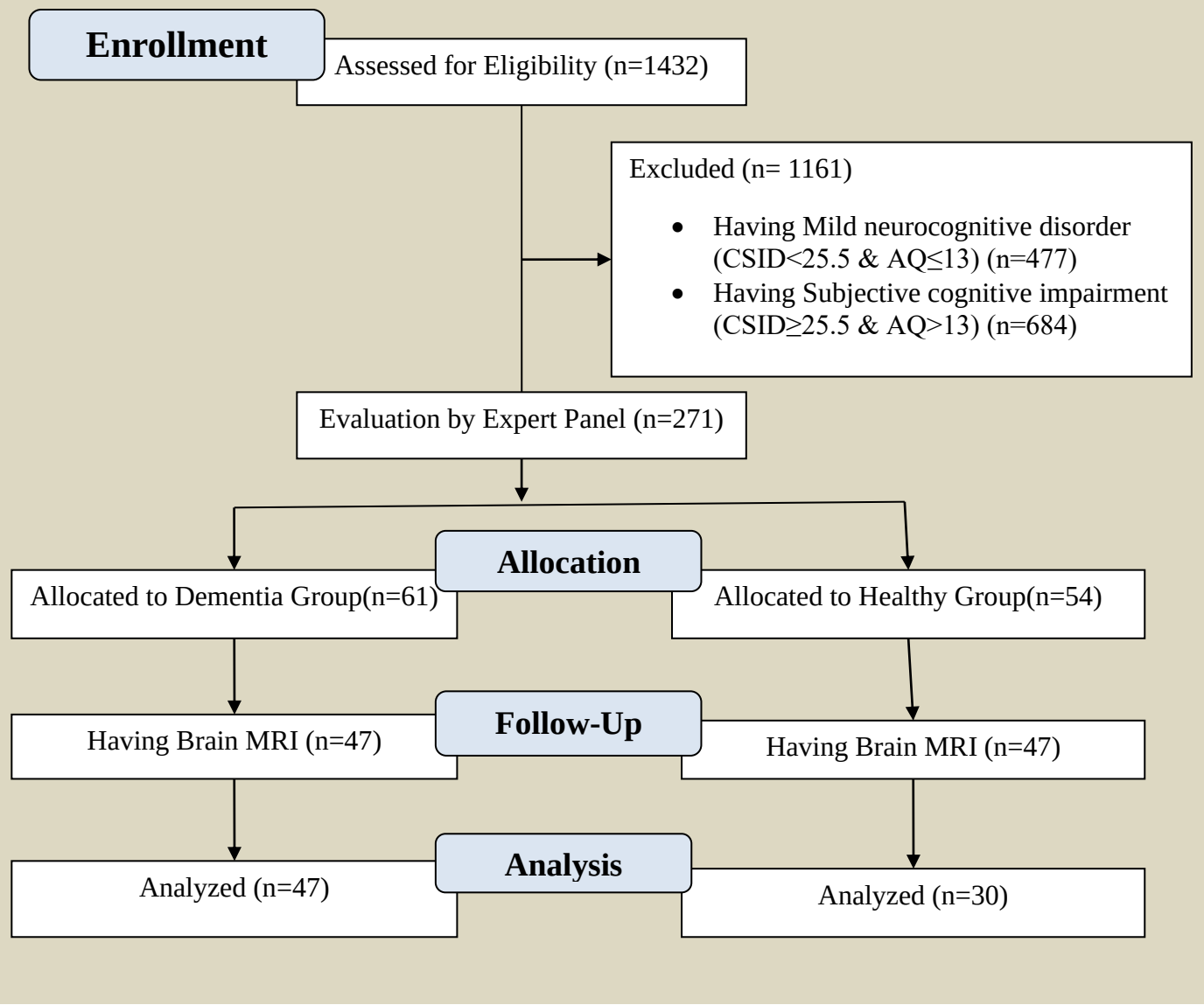
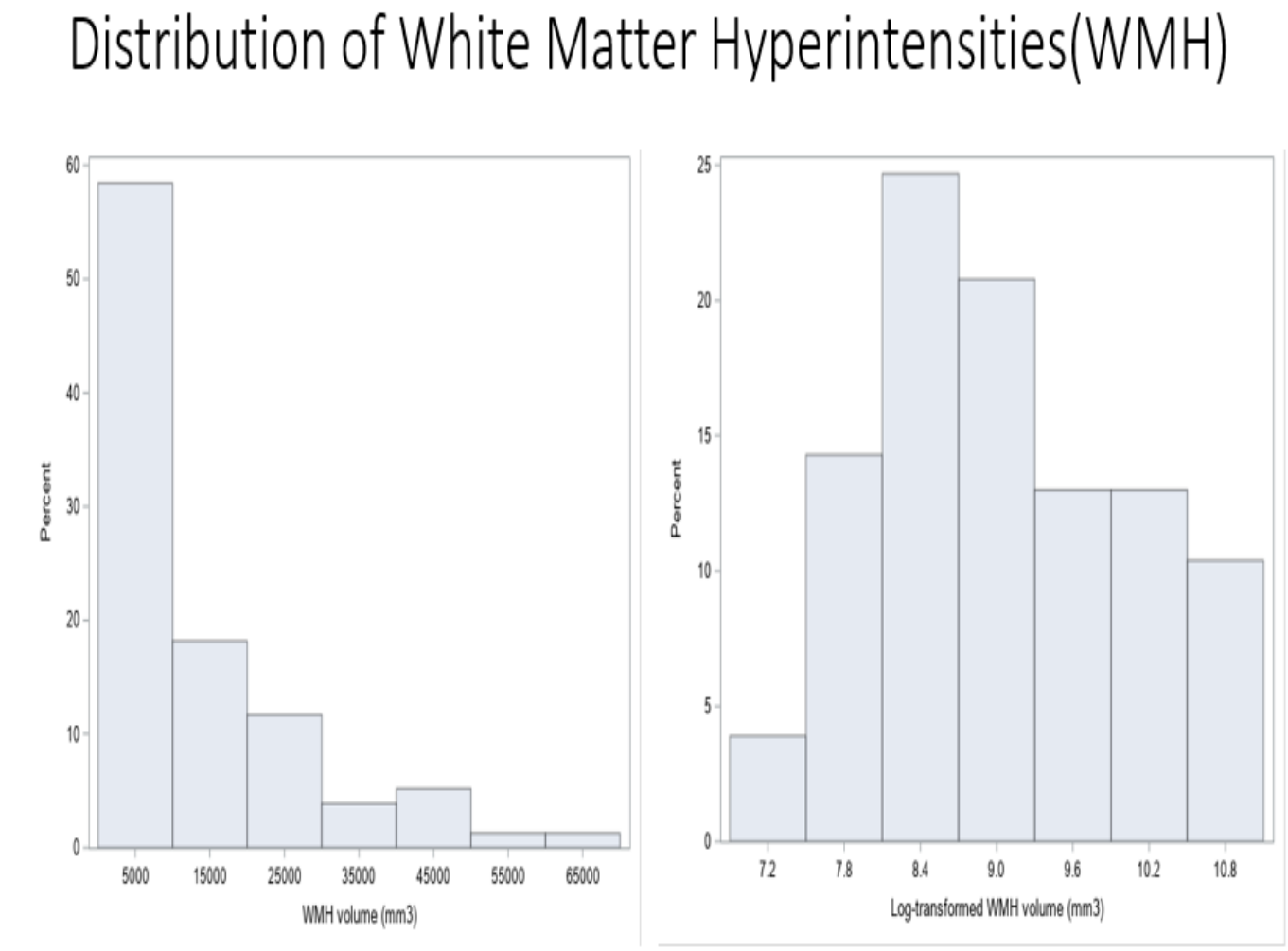


Figure 2


Distribution of White Matter Hyperintensities(WMH)
Percent
WMH volume (mm3)
5000
15000
25000
35000
45000
55000
65000
Log-transformed WMH volume (mm3)
7.2
7.8
8.4
9.0
9.6
10.2
10.8