BMC Neurology

RESEARCH

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Cognitive impairment and blood biomarkers of renal dysfunction in high-risk Nigerian population, with special attention to women and diabetes

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Abstract

Background Sub-Saharan Africans and Afro-Americans face 2-to-8 times higher risk of dementia compared to Caucasians, with Nigerian people being the highest population-at-risk. Adding to this challenge, their unique lipid profile increases their susceptibility to type 2 diabetes mellitus (DM-2), which further raises the risk of cognitive impairment (CI) by 1.5 times. Recently, we demonstrated a strong Diabetes/Dementia tandem in Nigerians, with increased cognitive vulnerability in illiterate, short-height, and diabetic Nigerian women in the eye of the storm. The combination of factors within this population makes it the optimal scenario to understand the relationship between CI and DM-2.

Methods Here, we further studied the blood biochemical analysis of our Makurdi cohort and searched for correlations with standard anthropometric measures, educational level, cognitive status (as assessed with MMSE, 6-CIT) and DM-2.

Results CI was prevalent across all groups, with higher incidence in DM-2 subjects and a marked sexual dimorphism. Thus, women exhibited a greater risk, especially those with low educational attainment. In the search for potential blood-based biomarkers for cognitive function, we identified those related to renal function. In particular, elevated uric acid and urea levels were associated with poorer cognitive performance, highlighting a potential kidney-brain axis connection.

Conclusion Renal function blood metabolites in this Nigerian cohort have been identified as possible kidney-brain axis biomarkers of CI. Moreover, illiteracy, female sex, and DM-2 pose them a compounded risk of developing CI. These findings advocate that targeted interventions addressing educational disparities and metabolic health could be proposed to mitigate cognitive decline in these vulnerable sub-groups. The integration of these factors provides a comprehensive understanding of CI incidence in Nigeria's population, offering new avenues for diagnosis, prevention, and treatment strategies.

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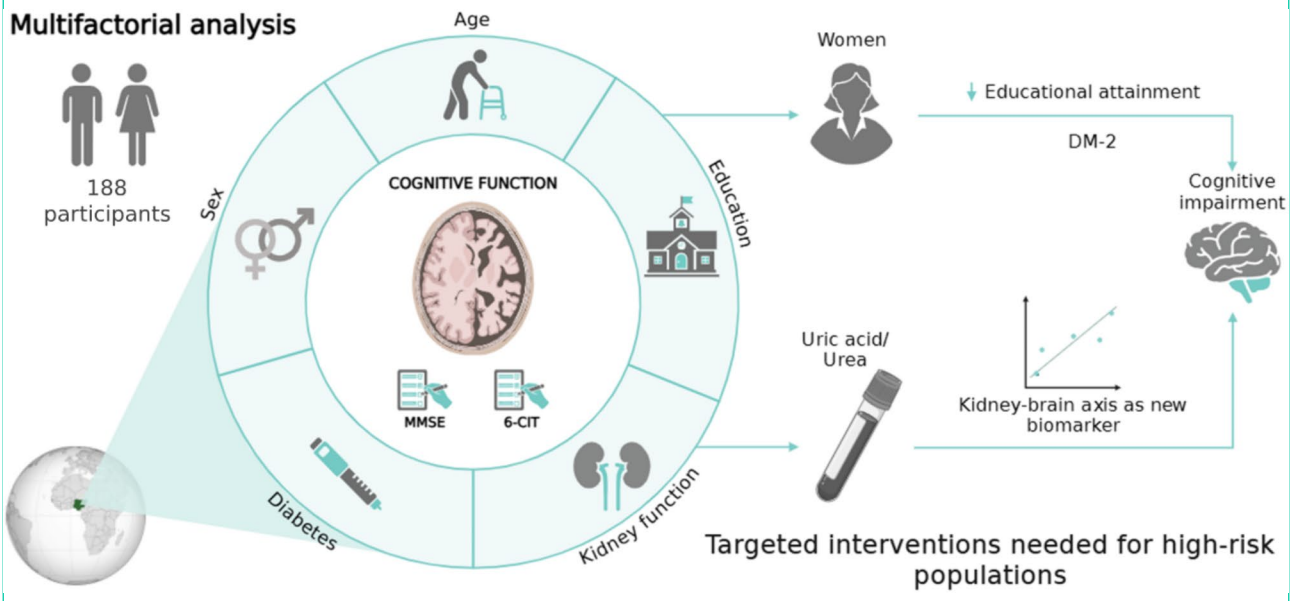
Clinical trial number Not applicable.

Graphical Abstract



Keywords Sub-Saharan Africa, High-risk AD, Kidney-brain axis, Biomarkers, Women

Background

Global dementia prevalence is projected to triple by 2050, with a clear geographical disparity: two-thirds of those affected will live in low- and middle-income countries [1]. In Nigeria the prevalence of dementia is estimated to range from 2.29 to 6.4% [2]. Cases have been increasing significantly over the past two decades. Rising from 63,512 in 1995 to 318,011 in 2015 among individuals aged 60 and above [3]. Key risk factors include advanced age, female sex, low body mass index [4]. Additionally, hypertension and diabetes mellitus type 2 (DM-2) have been also identified as important risk factors, with their prevalence increasing in Nigeria [5].

Our precedent results provided the first evidence of the association of short body height or stature and lower educational level profiles with poor cognitive performance in Nigerian women with DM-2 [6]. The present work aims to further study the relationship between cognitive performance and changes in detectable metabolites in blood both in normal and pathological conditions.

Within Nigeria's population obesity, metabolic abnormalities, and BMI-metabolic-risk sub-phenotypes have been described and this profile is closely related to DM-2 [7–9]. Metabolic, structural, and functional changes produced by DM-2 include cerebral insulin resistance, vascular endothelial dysfunction, inflammation, and blood-brain barrier injury, eventually leading to cognitive impairment (CI) [10]. DM-2 can affect the central nervous system indirectly through peripheral vascular disturbances that have been linked to CI [11]. In addition, peripheral oxidative stress and inflammation are also altered during DM-2 and influence cognitive status, playing an important role in CI [12–14]. A high prevalence of mild cognitive impairment (MCI) has been found among DM-2 patients, being a risk factor and promoting cognitive deterioration to evolve into dementia [15]. Therefore, early treatment is necessary for patients with DM-2 with MCI to improve their prognosis [16]. Despite research consistently demonstrating a significant relationship between DM-2 and CI, this relationship needs further study to unveil the working mechanisms between the periphery and the cognitive performance.

Given the racial predisposition to metabolic conditions linked to DM-2 and the associated increased risk of dementia, Nigeria faces a concerning public health challenge. As one of the countries in sub-Saharan Africa with a high prevalence of DM-2, the potential rise in DM-2-related dementia cases poses a significant threat to the population [17]. The sustaining increase in life expectancy in Africa requires active preventive measures against non-communicable diseases [18]. In particular, the prevalence of DM-2 in Nigeria has increased considerably over time and has become a problem adding strain to their healthcare system. We have proposed that an integrated

approach that considers all factors related to the pathogenic mechanisms of DM-2 and dementia is needed [18, 19]. This tandem diabetes/dementia is a new field yet not fully understood that needs research endeavors [20].

For that purpose, the blood analysis records obtained from the subjects of our precedent work were analyzed. This may contribute to shedding more light on the pathogenic mechanisms of the disease and new tools for monitoring and detection as well as risk factors for dementia. Research in the relationship between DM-2 and CI in the Nigerian population can provide scientific evidence for healthcare policies to design interventions tailored to the specific needs of this population.

Methods

The Makurdi cohort consisted of a total of 188 adult female and male subjects, studied from October 2017 to November 2018. Of them, 89 (52 women, 37 men) had at least 1 year of DM2 diagnosis, whereas 99 (53 women, 46 men) were healthy controls recruited at the Benue State University Teaching Hospital Diabetic Clinic and among the staff, respectively.

The study was approved by the Ethics committee of the Benue State University Teaching Hospital, Makurdi, Nigeria (PICDM2-NGN2017/0223). It adhered to the ethical principles for medical research involving human participants of the declaration of Helsinki. All the participants provided signed and written informed consent. Subjects who were illiterate had study plans interpreted in their local languages (Tiv, Idoma, Igede, Hausa) before their signed consent was taken and included in the study. The anonymity of participants was guaranteed, and the statistical analysis was performed by a researcher blind to the experiment.

For this study, the previously formed groups [6] were segregated according to the CI, determined for all the subjects using the Six-item Cognitive Impairment Test (6-CIT) and Mini-Mental State Examination (MMSE) scales. Participants were classified as cognitively normal if they scored <7 on the 6-CIT and/or >25 on the MMSE. Scores ≥ 8 on the 6-CIT and/or ≤ 24 on the MMSE indicated possible cognitive impairment (possible CI). The score of those tests was also correlated with the blood markers to determine the relationship between blood biomarkers and CI.

Blood analysis records were obtained to identify possible markers of CI with and without DM-2. In the case of healthy controls, the blood test was standard, measuring fasting blood glucose (FBG), Total cholesterol (TC), and uric acid. In the blood test of DM2 subjects, a more complete analytical profile included FBG, TC, high-density lipoproteins (HDL), low-density lipoproteins (LDL), urea, and creatinine. In addition, simple linear regression analysis was performed to determine the relationships between biochemical analysis and cognitive status.

Finally standard anthropometric measures, already shown in the previous work [6], were re-evaluated according to this CI segregation. Namely: Their body weight, height, waist circumference (WC), hip circumference (HC), body mass index (BMI), calculated by weight (Kg)/height (meters square), and waist-hip ratio (WHR), determined from WC/HC.

Statistical analyses were performed using GraphPad Prism 8.0. Fisher's exact test (one-tailed) was used to assess the association of DM-2 and CI prevalence. Two-way analysis for multiple variables (ANOVA) followed by Tukey's post hoc test for multiple comparisons or Student's t-test were used to assess the significance of differences between two independent groups. In all tests, statistical significance was set at $p \leq 0.05$.

Results

Cognitive impairment prevalence

CI was detected in the sampled population. It was present in all groups (Fig. 1, A and B) but the incidence was higher in DM-2 subjects, with a clear sexual dimorphism. The incidence of CI in men went from 14.13% in controls to 17.57% in DM2 while in women it went from 15.09 to 24.04% (Fig. 1, B, $p = 0.0464$, OR = 2.141, $N = 105$). The incidence of CI was closely related to the level of education of the subjects (Fig. 1, C and D). Women without education were the ones who obtained the worst scores, and as we ascend in level of education it is observed how the scores move away from CI towards a normal state.

Blood metabolite levels with cognitive impairment

Blood metabolite levels showed differences according to CI and DM-2. Levels of FBG, while within normal values, exhibited an interaction between sex and CI (Fig. 2, A, $F(1, 95) = 5.5$, $p = 0.021$), with a decrease of the levels observed in men with CI. This decrease was not present in women. In subjects with DM2, who exhibited FBG levels above normal, a similar interaction between sex and CI was observed (Fig. 2, D, $F(1,85) = 4.186$, $p = 0.0438$). The reduction in FBG levels in DM2 men with CI contrasted with an increase in DM2 women with CI, and this difference was significant. Lipid metabolism also displayed changes. TC levels were lower in CI subjects compared to those without CI (Fig. 2, B, $F[1, 49] = 4.8$, $p = 0.033$). However, this effect was absent in DM2 subjects, where women exhibited greater variability in TC levels. Among DM2 subjects, HDL levels were consistently below normal across all groups and showed considerable variability, whereas LDL levels remained within normal ranges. Renal function was also affected. Uric acid levels were increased exclusively in women with CI (Fig. 2, C, $F(1,89) = 6.17$, $p = 0.015$), with values reaching

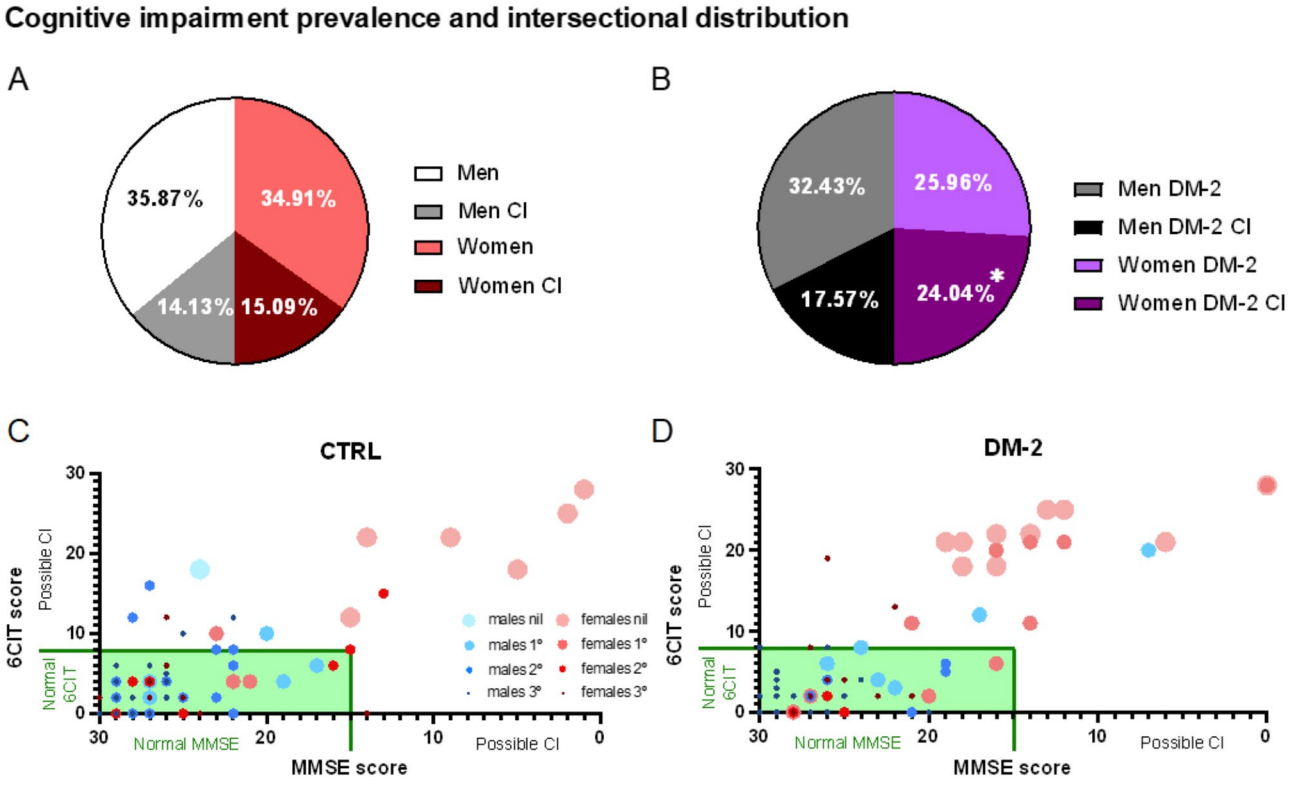


Fig. 1 Cognitive impairment prevalence across the sampled population. Diagrams showing the percentage of cognitive impairment prevalence in men and women, controls (**A**) and DM-2 (**B**). Intersectional representation of both cognitive tests for healthy control (**C**) and DM2 (**D**) subjects according to the levels of education (level of studies: no education (nil), primary education (1º), secondary education (2º), and tertiary education (3º)). The green box shows the normal score (6-CTI, score < 8; MMSE, score > 24). Association between CI and DM-2 in women, * $p \leq 0.05$

the upper limit of the normal range. In DM2 subjects, renal function was assessed by urea and creatinine levels, with no significant differences being observed. But, as with TC, women demonstrated greater variability. Some women with CI showed elevated levels of both urea and creatinine.

Aging, cognitive impairment and renal function correlations

Correlations between cognitive performance, age, and blood markers were performed. Relationships between the score of both cognitive tests and both age and blood markers of renal status were found in control and DM-2 subjects (Fig. 3, A-F). Results were similar for both controls and DM-2 subjects. CI scores correlated with older ages, with this relationship being more significant in DM-2 subjects (Fig. 3, A, all F's $(1,97) > 8.712$, $p < 0.004$; Fig. 3, B, all F's $(1,87) > 12.07$, $p < 0.008$). Moreover, a slight tendency of poorer cognitive performance with high levels of uric acid, in the case of the control subjects (Fig. 3, C), and urea, in the case of the DM-2 subjects (Fig. 3, D) was observed by its regression curves, moving from normal scores to possible CI scores. Results showed that these changes in both markers were not related to age (Fig. 3, E and F).

Antrhopometric measures with cognitive impairment

Anthropometrical levels showed differences according to CI. In the control group differences were found when separating the subjects into normal and CI subjects. Participants with possible CI had significantly lower body weight (Fig. 4, A, $F(1, 95) = 4.422$, $p = 0.0381$). BMI differences were sex-dependent, with women exhibiting higher values than men (Fig. 4, B, $F(1,95) = 10.24$, $p = 0.019$). Subjects with DM2 did not show significative differences in anthropometrical measures between subjects with normal cognitive status and subjects with possible CI.

Discussion

Educational levels as risk factor of cognitive impairment in Nigerian women, increasing with DM-2

The prevalence of dementia in Nigeria has been increasing over time, without fully understanding the reasons [3]. Some research attributes this increase in prevalence in racialized and minoritized groups to poorer outcomes due to genetics, culture, and/or health behaviors [21]. A new and exciting intersectoral field has emerge within psychiatry and neurology named geopsychiatry/neurology, which seeks to explore the impact of societal and environmental factors such as climate changes,

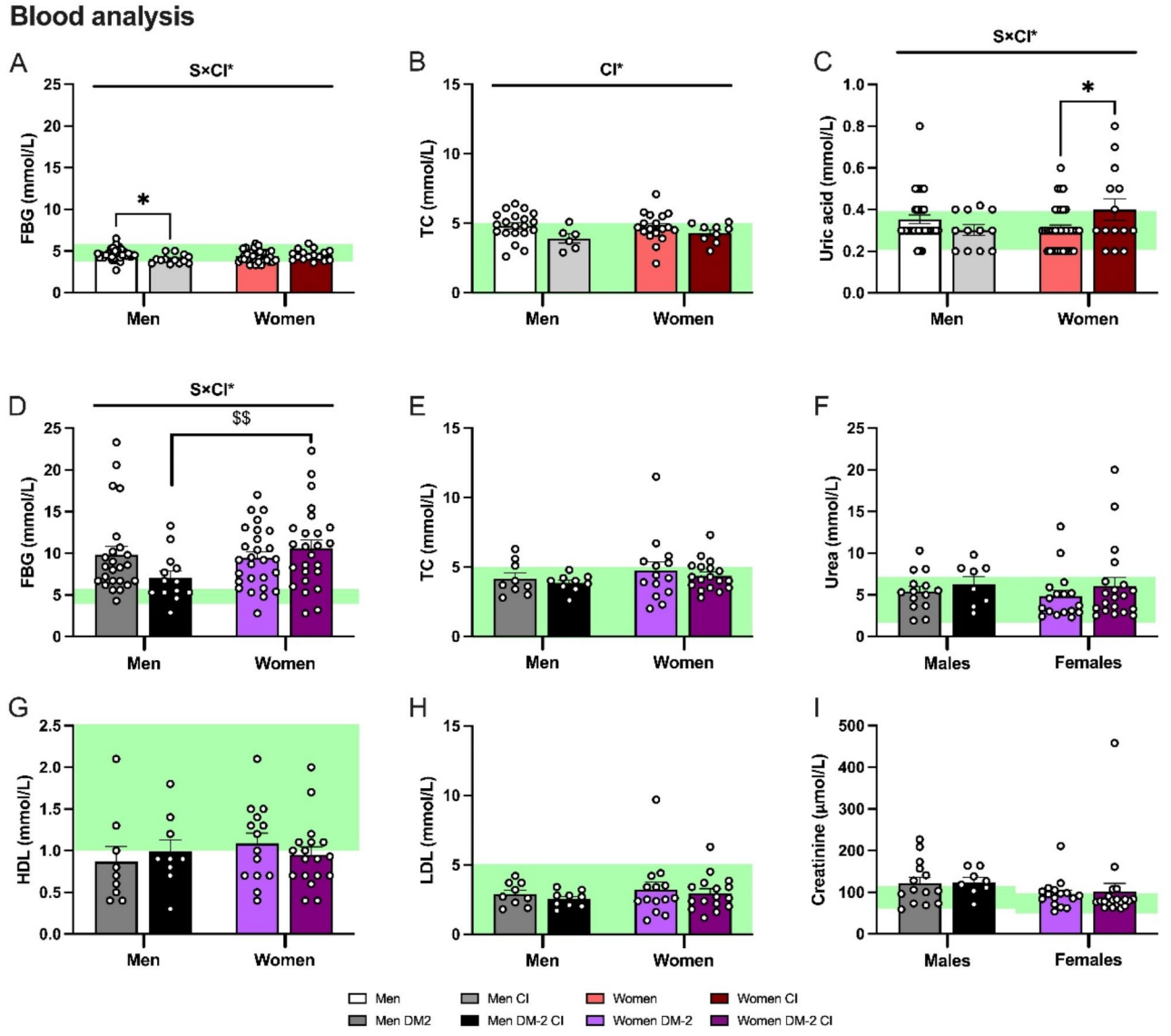


Fig. 2 Blood metabolite measures. Control subjects: FBG (**A**), TC (**B**) and uric acid (**C**). DM2 subjects: FBG (**D**), TC (**E**), urea (**F**), HDL (**G**), LDL (**H**), and creatinine (**I**). Green boxes show normal levels in blood. $N = 12–37$ subjects per group, mean ± SEM. Cognitive impairment: CI*, $p \leq 0.05$. Factor interaction effect: sex and cognitive impairment: S × CI*, $p \leq 0.05$. Differences between two counterparts, sex: $^{\$\$}p \leq 0.01$; Cognitive impairment: * $p \leq 0.05$

globalization, socio-economic development and cultural practices on the mental health and mental illness processes [22].

Advanced age and low educational level are considered risk factors for dementia. Sex and body mass index are also important factors in developing dementia [4]. In previous results, short height and poor educational levels were considered risk factors for CI in Nigerian women [6]. In the present analysis, CI was present in healthy and DM-2 subjects. The population distribution-based analysis showed a sex-dependent intersection between cognitive performance and educational levels, with uneducated women having the poorest cognitive status in normal and DM-2 conditions. Moreover, DM-2 caused the distribution to move away from normal cognitive scores. The results also showed a rise in the prevalence of possible CI in DM-2 subjects, especially in women. This would be in agreement with other studies showing the relationship between DM-2 and CI [23]. Our study, conducted within this specific ethnic context, supports the notion that low educational attainment is a significant risk factor for dementia. It particularly highlights the vulnerability of Nigerian women, who face a higher risk of developing dementia due to limited access to education. This risk is further amplified if they are diagnosed with DM-2, underscoring the urgent need for targeted interventions to address these intersecting health and social challenges.

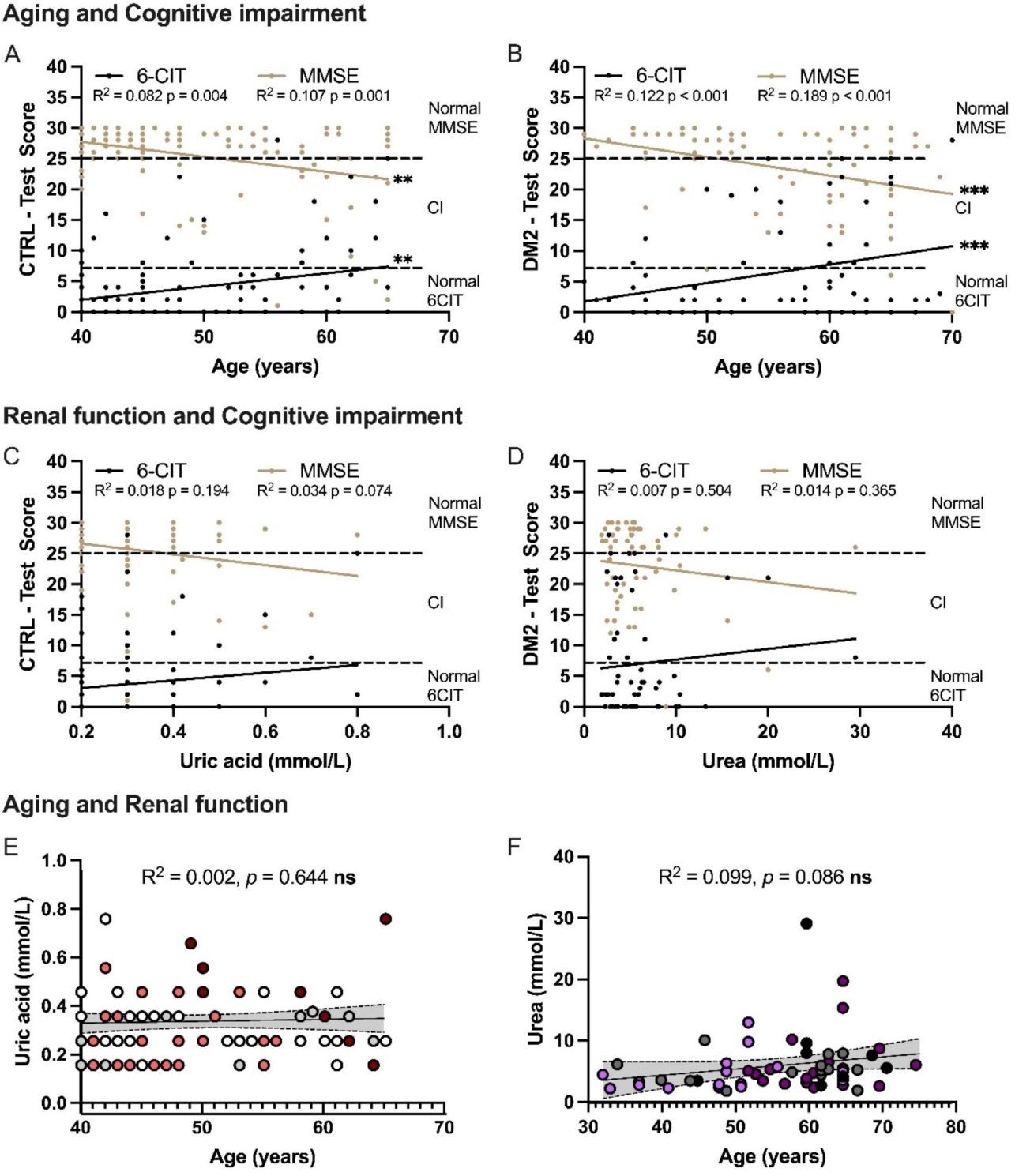


Fig. 3 Scattered plot representing correlations of Aging (age of subjects), Cognitive impairment (both test 6-CIT and MMSE), and renal function (Uric acid and Urea levels in the blood). Correlation between age and cognitive impairment in control subjects (**A**) and DM-2 subjects (**B**); correlation between the levels of uric acid in control subjects (**C**) and Urea in DM-2 subjects (**D**) with cognitive impairment; correlation between age and the levels of uric acid in control subjects (**E**) and the levels of urea in DM-2 subjects (**F**). Simple linear regression was performed, ** $p < 0.01$; *** $p < 0.001$

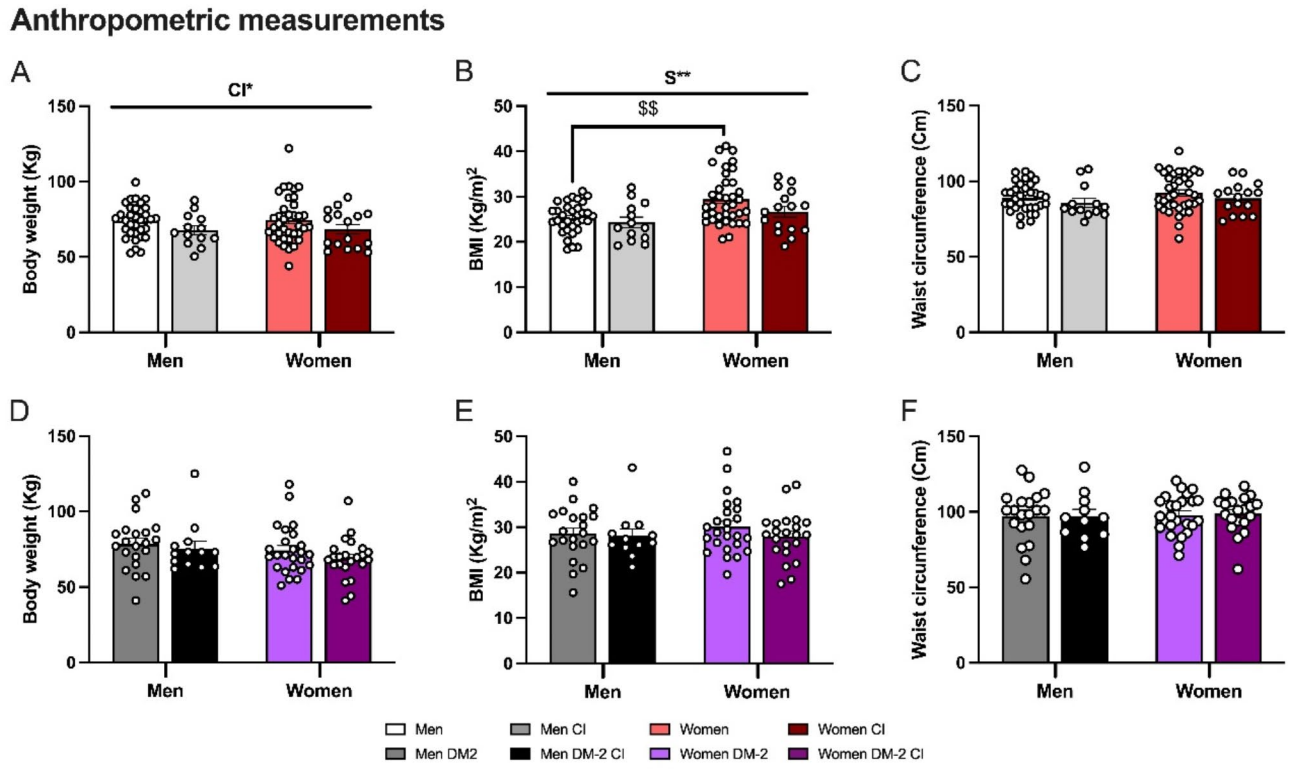


Fig. 4 Anthropometric measurements for control subjects of Body weight (**A**), BMI (**B**), Waist circumference (**C**); and DM2 subjects Body weight (**D**), BMI (**E**), Waist circumference (**F**). Green boxes show normal levels in blood. $N = 12–37$ subjects per group, mean ± SEM. Cognitive impairment: CI*, $p \leq 0.05$. Sex, S**, $p \leq 0.01$. Interaction effect: sex and cognitive impairment: S × CI*, $p \leq 0.05$. Differences between two counterparts, sex: $^{\$\$}p \leq 0.01$

Blood markers of cognitive impairment

Analyzing blood markers and their relationship to cognitive function under normal and pathological conditions can help to understand the etiology and development of CI, and how it translates at the peripheral level. In the present work, we show that signs of CI - measured by any of the two tests- were associated with slight alterations in metabolites measured in standard blood test routines such as glucose profile, lipid profile, and renal function.

The glucose profile followed the hallmark changes associated with DM-2, with individuals diagnosed with DM-2 showing higher FBG levels due to hormones imbalances caused by the disease [24]. Interestingly, control and DM-2 subjects with possible CI presented sex-dependent changes in FBG levels, with lower levels in men and slightly higher levels in women.

Regarding the lipidic profile, TC levels were slightly reduced in CI. Although the TC levels remained within normal values, they are interesting to note since low levels of TC have been related to a higher mortality risk [25]. Additionally, in the DM-2 subjects, all lipidic profile including HDL and LDL were measured. LDL levels, as was the case with TC levels, presented a slight reduction when there was CI, still within normal values. However, the effect on HDL levels was clearer, being below normal blood values. This was to be expected as low HDL levels have been consistently linked to increased risk of DM2 [26]. In fact, a high prevalence of low levels of HDL has been found among DM-2 patients [27]. Moreover, having possible CI had slight sex-dependent effects, increasing HDL levels in men, and decreasing them in women, the opposite trend that was observed in FBG.

Uric acid levels are a marker of renal function, and high plasma levels of uric acid are also associated with high plasma levels of glomerular function markers such as urea and creatinine [28]. Due to methodological reasons in clinical routines, in the analytical analysis obtained from control subjects, renal function was measured by uric acid levels, whereas urea and creatinine levels were analyzed from blood samples from DM-2 subjects. The uric acid levels in control subjects were within the range of normal values, however, women with CI presented an increase in the levels, positioning themselves in the upper limit of normal values, thus indicating a possible relationship between uric acid levels and CI. Studies on the possible relationship between uric acid levels and CI have not been conclusive and there is still a lack of knowledge about the role of uric acid in CI. Some authors state that high levels of uric acid may be related to a lower risk of dementia and better cognitive performance, possibly due to its antioxidant action [29] and low levels of uric acid represent a risk factor for mild CI [30]. This is

inconsistent with the results which showed the highest levels of uric acid in women with possible CI. However, other studies support the idea that high uric acid levels have a detrimental effect on cognitive function, especially when these elevated levels are prolonged over time [31, 32]. These effects have been observed in rats with hyperuricemia [33]. Moreover, in patients with chronic kidney disease, in whom uric acid levels are frequently elevated, these levels correlate with CI [34]. This is consistent with the results where high levels of uric acid showed a correlation with scores from both MMSE and 6-CIT indicating possible CI in control subjects. Uric acid seems to have a dual role as a protective or risk factor for CI. Thus, while within normal values it is considered an antioxidant protector, when levels are higher and hyperuricemia happens, it could be a potential risk factor for CI, mostly by increasing the inflammatory activity [35]. In DM-2 subjects, urea, and creatinine presented a slight increase in their levels in CI subjects, indicating that CI and DM-2 are affecting renal function. This was more marked in women in agreement with previous results positioning the female sex as a risk factor for dementia in the Nigerian population [6].

Aging, cognitive impairment and renal function

Correlation between the factors studied can bring light into the complex communication between different systems in CI processes. Results showed a clear correlation between aging and CI, with scores from both cognitive tests indicating clearer cognitive impairment at old ages. The aging process is a progressive accumulation of changes associated with diseases processes that all living beings experience as they grow old [36]. CI is one of those changes and the phenotype of this normal cognitive aging is well-defined, including reductions in processing speed, reasoning, memory, and executive functions [37]. This normal cognitive aging under pathological processes, such as DM-2, makes this decline more marked, as shown by the strong statistical significance of the correlation between the cognitive test scores and the age of the DM-2 subjects. Other studies have already concluded that DM-2 is associated with accelerated CI and neurodegenerative processes in old age [38]. Considering the high prevalence of DM-2 in Nigerian population, CI is an important aspect to take into account in this population.

Interestingly, renal function also showed fluctuations with cognitive status. There was a tendency with higher levels of markers of renal function towards cognitive impairment scores both in MMSE and 6-CIT tests. A meta-analysis conducted to study the relationship between uric acid levels and cognitive impairment in different subtypes of dementia revealed that uric acid levels were not related to MMSE scores except for Parkinson's disease-associated dementia [39]. Although uric acid is thought to have a protective effect towards the cognitive system in Alzheimer's disease and Parkinson's disease and a toxic impact on vascular disease dementia [40]. In this study, MMSE and 6-CIT revealed cognitive impairment scores tended to be from control subjects with high levels of uric acid. Moreover, elevated levels of uric acid from patients with chronic kidney disease receiving hemodialysis have been reported to contribute to cognitive impairment [41]. In addition, high levels of uric acid have already been linked to the brain as a possible marker of silent cerebral infarction, especially in women [42]. These findings reveal a bidirectional communication between renal function and cognitive status.

Pathological conditions, where a high prevalence of CI has been detected, can be an optimal scenario to analyze this communication, such as DM-2 [15]. In fact, results from this study showed an increase in the prevalence of cognitive impairment in DM-2 subjects, especially in women. Correlations showed that cognitive impairment scores from MMSE and 6-CIT tended to appear with high levels of urea. Studies have seen how diabetic patients had significantly higher levels of urea and creatinine in blood serum [43]. Considering the increase of these two metabolites in blood has been widely associated with kidney function failure [44], this positions DM-2 as a risk factor for kidney damage progression and these two metabolites as simple biomarkers as predictors and prognosis of renal failure in DM-2 [45]. Moreover, increased levels of urea have been reported in various types of dementia causing neurodegeneration [46, 47]. Along with cognitive impairment research also considers nephropathy, retinopathy, and neuropathy as recurrent complications in DM-2 [48], indicating the close relationship between cognitive function and renal function in these pathological conditions. The absence of a correlation of age with the levels of both uric acid and urea indicates that age is affecting CI but not the levels of these metabolites. Changes in the levels of these metabolites came from cognitive deficits, however the mechanisms behind this relationship remain unknown.

Study limitations

The variability of the sample was a fair representation of the real scenario in this population-based study, but the wide window of ages could be masking some results. The stratification of the sample according to age didn't show different trends, and for some ages, the statistical power was limited. Concerning cognitive tests, the 6-CIT test was included to solve any limitations of MMSE to detect early CI in DM-2, but other tests such as the P300 event-related potential could also be useful [49]. The results of the blood test records we obtained were limited by clinical routines and only considered metabolites related to cholesterol metabolism and renal function. Under an

integrative system analysis to understand body-brain function, it would be interesting to analyze metabolites related to other organs' functions as they may be also altered and correlated to cognitive dysfunction. Among them, transaminase levels for hepatic function may be indicative of derangements of the liver-brain axis in this population [50].

Conclusions

Although similar findings have been reported in other populations, this study is novel because it focuses on Nigerians, who have the highest risk of dementia among Sub-Saharan and Afro-American populations. Low educational attainment is a well-known risk factor for dementia, this study provides robust evidence of its impact in a specific ethnic and cultural context. It highlights the compounded risk when low education intersects with DM-2, particularly in women. Moving beyond cognitive and anthropometric measures, this study takes a more holistic approach by analyzing blood metabolites to better understand the metabolic changes linked to CI. Notably, it identifies elevated uric acid and urea as potential blood-based biomarkers for CI in the Makurdi cohort, opening new avenues for research into the kidney-brain axis as a possible tool for early diagnosis and intervention strategies. Finally, by integrating multiple risk factors – educational level, sex, DM-2 and metabolic markers – it provides a more comprehensive understanding of CI. From a geopsychiatry/neurology view, this multifactorial and intersectional approach is essential for developing targeted interventions and addressing the global burden of CI, offering valuable insights for both research and public health strategies.

Acknowledgements
The authors sincerely thank the Diabetic Clinic of Benue State University Teaching Hospital, Makurdi, Nigeria. Also, the authors thank Professor Moses Msugh Kembe, Vice-Chancellor, Benue State University, Makurdi, Nigeria, for institutional support for the project while it lasted. The authors are also grateful to the management and staff of the Benue State University Teaching Hospital, Makurdi, Nigeria, for their support in subjects' recruitment and blood analyses during the study.

Author contributions
Conceptualization, L.G.-L.; experimental design performance, L.G.-L.; harvesting, bio-chemical analysis: F.D., M.O. and E.K.O.; data analysis and statistics: J.F.-R; illustra-tions: J.F.-R.; writing—original draft preparation, J.F.-R.; writing—review and editing, J.F.-R. and L.G.-L.; funding acquisition, L.G.-L and E.K.O. All authors have read and agreed to the published version of the manuscript.

Funding
This work was supported by personal fundings and FAS, Fundació Autònoma Solidaria, Fons de Solidaritat de la UAB, UAB Solidarity Fund, FSXXXIV-03, University cooperation projects for development of countries of the South: Prevalence of Cognitive Impairment in Nigerian Subjects with Diabetes Mellitus Type 2 and Associated Comorbidities to L.G.-L, with E.K.O as counterpart in Nigeria.

Data availability
The data presented in this study are available on request to the corresponding author.

Declarations

Ethics approval and consent to participate
Yes, the study was approved by the Ethics committee of the Benue State University Teaching Hospital, Makurdi, Nigeria. It adhered to the ethical principles for medical research involving human participants of the declaration of Helsinki. All the participants provided signed and written informed consent. Subjects who were illiterate had study plans interpreted in their local languages (Tiv, Idoma, Igede, Hausa) before their signed consent was taken and included in the study. The anonymity of participants was guaranteed, and the statistical analysis was performed by a researcher blind to the experiment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 25 February 2025 / Accepted: 1 April 2025
Published online: 11 April 2025

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