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Diagnostic Assessment & Prognosis

Short height and poor education increase the risk of dementia in Nigerian type 2 diabetic women

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Introduction: There is urgent need to investigate type 2 diabetes and dementia crosstalk in sub-Saharan African countries with special attention to women who have higher vulnerability. Nigeria which has the highest number of diabetics on the African continent is a good location for the investigation.

Methods: Biophysical parameters, occupation, education, burden of diabetes mellitus, cardiovascular health, and cognition were evaluated in 102 type 2 diabetics and 99 controls.

Results: Short physical stature and lower level of education were hallmarks of diabetes in females. Two dementia scales (Mini–Mental State Examination and six-item Cognitive Impairment Test) showed cognitive impairment status, with the six-item Cognitive Impairment Test scale being more specific and sensitive. Both scales showed correlations with age, education, weight, height, and disease onset, whereas fasten blood glucose was negatively correlated with height and their blood pressure was normal.

Discussion: Height, an easy-to-measure parameter in Nigeria, may reveal increased risk of dementia in poorly educated female Nigerian diabetics, thus helping to improve preventive and therapeutic interventions.
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1. Introduction

Nigeria has the highest number of diabetics on the African continent [1], and this is due to rising mean age of the population and prevalence of obesity, hypertension, and widespread adoption of sedentary lifestyle. Diabetes mellitus type 2 (DM2) in midlife is a risk factor for dementia, and this association is stronger in persons of African ancestry [2–4]. Occurrence of DM2 in midlife and other factors listed previously are known to accelerate development of dementia in Africa Americans [2,5] compared with Caucasians [2–4,6–8]. It is worrisome that the prevalence of DM2 will increase astronomically in the next few years; with 75% of the cases living in low-to-middle–income countries (LMICs), including Nigeria [1]. The World Alzheimer Report 2015 states that 58% of the global 46.8 million dementia patients live in LMICs [9], and this is expected to reach 63% in 12 years with a concurrent huge socioeconomic cost [9,10]. This cost, which is reported to be enormous in developed economies, will be devastating and unsustainable for the health care system of Nigeria; a country that is witnessing rapid rise in diabetes prevalence [10,11]. Between the 1960s and recent time, the prevalence of diabetes increased from less than 1% to about 10% in Nigeria [11].

Some investigations have shown that dementia is 1.5 times more common in females and it is even worse in sub-Saharan Africa women with a two- to eight-fold increased risk [12]. A combination of aforementioned factors could

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lead to a "dementia boom" in Nigeria and the subregion, if they are not proactively managed. Hence, there is urgent need to investigate the factors associated with the crosstalk between DM2 and dementia in persons of African ancestry with special attention to women who are more susceptible to dementia. Such efforts will help in the development of evidence-based management approaches in relevant clinics and communities of Nigeria and the subregion.

2. Methods

A total of 208 adult female and male subjects—109 (62 female, 47 male) with DM2 and 99 (53 female, 46 male) healthy controls—were recruited, at the Diabetic Clinic of the Benue State University Teaching Hospital, Makurdi, Nigeria, and among Benue State University Teaching Hospital and Benue State University staff, respectively, from October 2017 to November 2018.

Standard anthropometric measures of body weight (kilogram), height (centimeters), waist circumference (WC in centimeters) and hip circumference (HC in centimeters) were recorded in both patients with DM2 and controls. Their body mass index (BMI) was calculated by weight (kg)/height (meters square), and waist-hip ratio (WHR) was determined from WC/HC, in both groups. The burden of DM2 was measured as fasting blood glucose (FBG), duration and onset of disease. Systolic (SBP) and diastolic pressures (DBP) were measured for the evaluation of the cardiovascular health of the subjects.

Six-item Cognitive Impairment Test (6-CIT) and Mini–Mental State Examination (MMSE) scales were used for the comparative assessment of cognitive status of the subjects. Anonymity of the participants was guaranteed, and the statistical analyses were carried out by a researcher blind to the experiment. The study was approved by the Ethics Committee of the Benue State University Teaching Hospital, Makurdi, Nigeria. All the participants provided signed and written informed consent. Subjects who were illiterate had the study plans interpreted in the local languages (Tiv, Idoma, Igede, Hausa) before their signed consent was taken and included in the study.

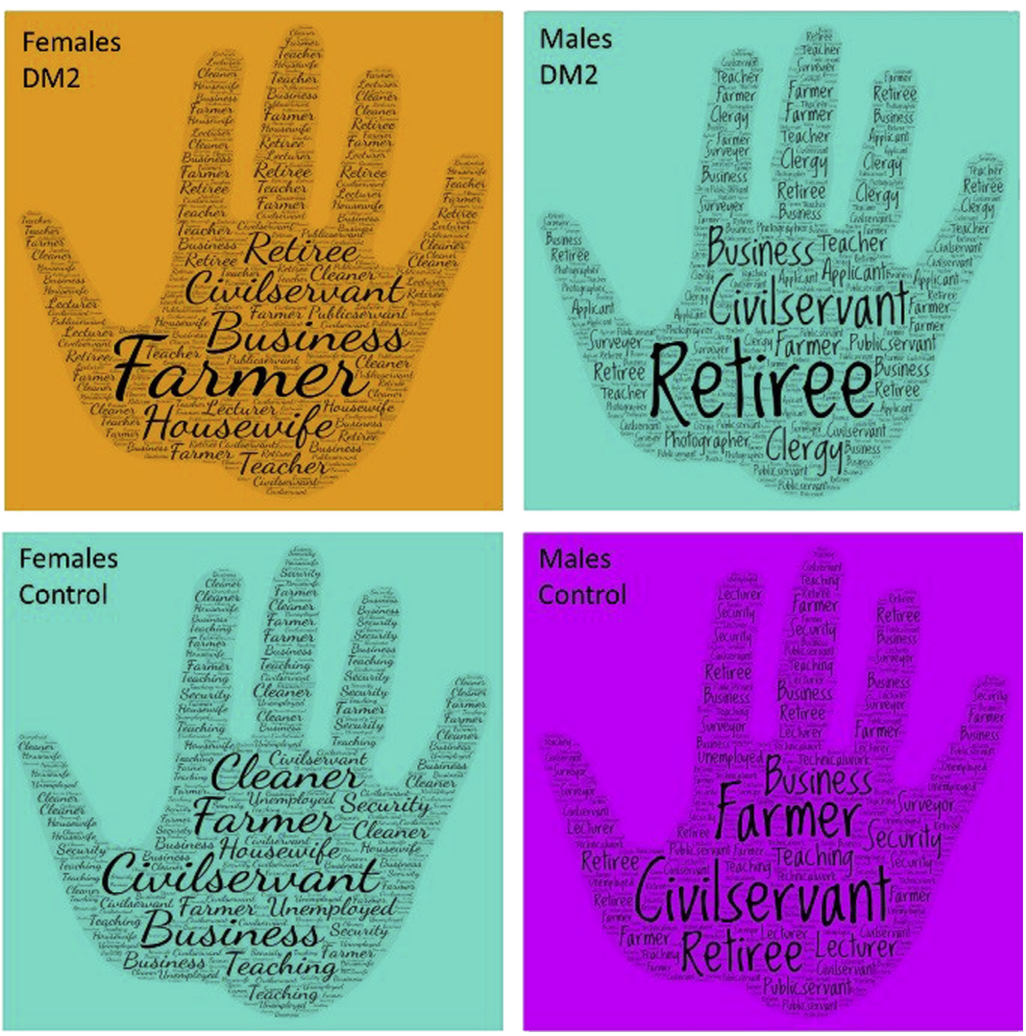

Fig. 1. Tag clouds of the occupational status of the four groups in the Nigerian sample population.

Statistical analyses were performed using SPP15.0. A two-factor (DM2 and sex) factorial analysis was used to analyze the effect of the disease and sex interactions in the population. Two-way analysis of variance followed by Duncan's *post hoc* or Student *t*-test was used to analyze differences between the groups. Pearson's correlation was used to identify relationship between demographic, anthropometric, and disease variables with statistical significance considered at $P < .05$.

3. Results and discussion

The recruitment of patients attending a diabetic clinic and controls from two adjacent establishments provided a sample population with different occupations and cadres (Fig. 1). Around 45.2% of the study subjects were either civil servants or its retirees. The other subjects were from varied vocations, including farming, clergy, cleaning services, technicians, and housewives. Among the DM2 group, the most common occupation was farming (females: 30.7%), followed by retirees (males: 36.2%). In contrast, civil service was the most common occupation of the control subjects (females: 47.2%; males: 21.7%). Similar to previous reports in hospital-based studies in Nigeria, patients with DM2 in this study were 5-6 years older than their healthy controls (P = .000). There was no age difference between sexes in both diabetic and control populations (Fig. 2A).

The distribution of level of education in the sample population (Fig. 2C) did not show a standard normal probability distribution. When the study groups were combined, analyses showed that more than 50% of the subjects obtained a tertiary level of education (females-DM2: 53.2%, males-DM2: 66.0%, females-controls: 62.3%, and males-controls: 58.7%). However, the distribution of participants with low levels of education differed between sexes. The sex of the subjects were related to their level of education attainment, with diabetic women being least educated compared with the other groups (Fig. 2B,C). Illiteracy, which means the absence of any formal education, was more common in the female patients with DM2. The males, irrespective of disease status, had a higher level of education than the females (P = .030). In contrast, a statistically significant higher percentage of female subjects were illiterate compared with males. Illiteracy among diabetic females (females-DM2: 22.6%) was increased two-fold compared with their control counterpart (females-controls: 11.3%) but was 11-fold higher than diabetic males (males-DM2: 2.2%) and controls (males-controls: 2.1%). Thus, the diabetic females had the lowest level of education, whether at a primary or secondary level. Therefore, sex may be a key factor for education achievement in Nigeria. The association of educational attainment and dementia is long established, even in places where there is lower access to education [13]. It is known that exposure to education increases the cognitive reserve of individuals. This is achieved through neuroplasticity and development of functional and complex neural networks that come with a higher level of education attainment and activities. The enhanced cognitive reserve helps the patient to compensate for greater degrees of neuropathology that may occur in later life; hence, education is identified as a proxy for such reserve in various investigations [13]. Education in early life appears to disconnect observed degree of neuropathology and cognitive impairment in later life. This disconnection is reiterated by findings in some individuals able to tolerate greater disease burden without corresponding evidence of clinical dementia [14]. Furthermore, in addition to age and complications of diabetes, education is an integral component of a key predictive tool for a 10-year likelihood of dementia [15].

Age was negatively correlated with education in this study. The mean age of the subjects in the DM2 group was higher than that of the controls, possibly due to recruitment bias. The authors relate this finding to the higher number of retired subjects in the diabetic group. There was no significant age difference between the sexes, although the age was lower in the females. This can be interpreted to suggest that the Nigerian females become diabetic at earlier ages.

Sex is a key factor for education achievement in this population as indicated previously. In our opinion, early childhood education or even adulthood education activities, especially for females, may be a preventive policy to adapt for mitigation of later life cognitive impairment in this population. The factors of age and education correlated with onset of disease, systolic pressure, and cognitive impairment when measured by both dementia scales used in the study. Also, the factors are related to anthropometric measures of WC and WHR, parameters which clinical guidelines advise should be measured in diabetic clinics. Similarly, education was related to body weight and height in the whole study population.

Anthropometric measures showed a strong relationship with diabetes (Fig. 2D–G). The BMI (P = .004)—but not body weight—WC (P = .000), and WHR (P = .000) were significantly associated with FBG in DM2, but not in the healthy controls (see Supplementary Table 1). Body height was the most specific and distinguishing variable of the different groups, especially by DM2 (P = .000) and sex (P = .000) status. The diabetic female group had the shortest height or stature. Reduced height in females was associated with DM2 in this Nigerian population. BMI (P = .001) and HC (P = .002) also showed differences between sexes. Height was strongly related to education, body weight, and BMI, but not to WC, HC, or WHR. Short height or stature in the Nigerian females may be due to exposure to worse early-life stress and poor nutrition, compared with the males. This is because, besides genetics, the above discussed risk factors are major contributors to adult height and other biophysical indices [16]. Short stature and patient sex may be dependent on the environment, as diabetic adult males were reported to be shorter in Israel [16], unlike what is observed in the females of this Nigerian population. The relevance of early-life nutrition interventions is supported by evidence that it increases the brain reserves and protect against later-life

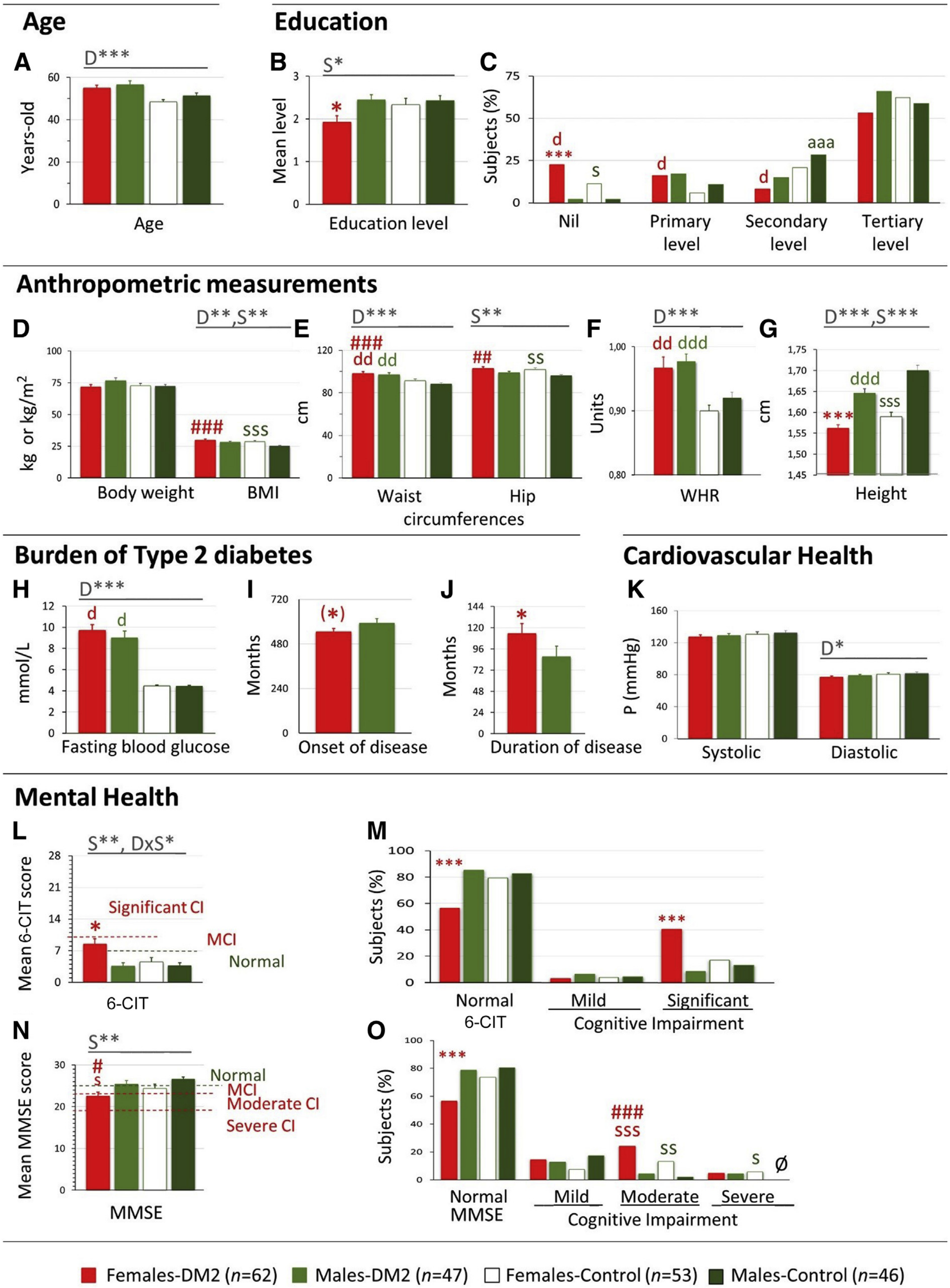

Fig. 2. Age, education, anthropometric measurements, and burden of diseases in the Nigerian sample population. (A) Age of the sample population. Education: (B) mean education level and (C) percentage of subjects at each level of education, from nil or no education to tertiary level education. Anthropometric measurements: (D) body weight and BMI, (E) waist circumference and hip circumferences, (F) WHR, and (G) height. Burden of DM2: (H) fasting blood glucose, (I)

neurodegeneration, through decrease in cardiometabolic risk factors [17]. This is consistent with the Barker hypothesis, which says that optimal prenatal and early-life environment increases the risk of adult disease [18]. The sub-Saharan Africa region has a high prevalence of low–birth weight babies. Low–birth weight babies have been shown to have poorer cognitive development, which may lead to even poor cognitive function in adulthood [19]. The present study is unable to confirm if the prevalence of low birth weight is more common in the female population of this study, or in the general population. However, a recent Nigerian study suggests that an equal number of male and female children are born with low birth weight [20]. Thus, the observed sex differences in height could be environmentally determined.

The burden of DM2 (Fig. 2H,I) measured as FBG levels (FBG, $P = .000$ vs. controls) and prevalence of disease (females-DM2: 21.3%; males-DM2: 23.4%) were similar in both sexes. However, duration of disease ($P = .000$) was longer in females than males, thus supporting earlier position that disease occurs earlier in women. On the average, DM2 occurred 4 years earlier in the females ($P = .05$, one-tailed).

The two scales administered to assess dementia (Fig. 2L–O) showed a strong effect of sex (6-CIT, $P = .005$; MMSE, $P = .004$) with diabetic females showing poorer cognitive performances than their male counterparts. A lower percentage of diabetic females were categorized as normal cognition compared with the others (Fig. 2M,O). Conversely, more diabetic females were found in the moderate to significant cognitive impairment category using the 6-CIT and MMSE scales. The 6-CIT scale was more discriminative than MMSE as it showed a disease and sex impact on measurement of cognition in this population. The MMSE only showed sex impact with the mildly impaired diabetic females in contrast to the diabetic males and controls found to be cognitively normal. Correlation analysis is shown in Supplementary Table 1. The two dementia scales showed correlations ($n = 208$) with age (6-CIT, r = .347, $P < .01$; MMSE, r = −.388, $P < .01$), education (6-CIT, r = −.750, $P < .01$; MMSE, r = .743, $P < .01$), weight (6-CIT, r = −.230, $P < .01$; MMSE, r = −.278, $P < .01$), height (6-CIT, r = −.262, $P < .01$; MMSE, r = .267, $P < .01$), and disease onset (6-CIT, r = .267, $P < .01$; MMSE, r = −.297, $P < .01$). FBG showed a negative correlation with height (r = −.104). The factors age and education correlated with onset of disease (age, r = .820, $P < .01$; education, r = −.293, $P < .01$), systolic pressure (age, r = .306, $P < .01$; education, r = −.180, $P < .01$), and cognitive impairment measured by both 6-CIT (age, r = .347, $P < .01$; education, r = −.750, $P < .01$) and MMSE (age, r = −.388, $P < .01$; education, r = .743, $P < .01$) scales. Age was also related to anthropometric measures of WC (r = .206, $P < .01$) and WHR (r = .271, $P < .01$), and these are parameters expected to be measured in diabetic clinics. Education was related to body weight (r = .197, $P < .01$) and height (r = .258, $P < .01$) in the whole study population. The FBG only correlated with systolic (r = −.162, $P < .05$) and diastolic (r = −.170, $P < .05$) measures for cardiovascular health. Onset of disease correlated with age (r = .820, $P < .01$), education (r = −.293, $P < .01$), systolic pressure (r = .219, $P < .05$), and cognitive impairment as measured by 6-CIT (r = .267, $P < .01$) and MMSE (r = −.297, $P < .01$).

The association of height with education attainment and the dementia scales in this population may be related to early-life circumstances, which were discussed previously. It is known that optimal nutrition in early infant life can improve cognitive and brain development throughout childhood and adolescence; periods that have significant implication for later-life biophysical and educational attainment [21]. The authors are of the opinion that if Nigerian public policy targets improvements of early-life nutrition and education programs, with emphasis on the girl child, the burden of dementia in adult diabetic females may be mitigated.

In conclusion, short body height or stature and lower education levels are hallmarks of diabetes in females in this Nigerian population. Most importantly, these factors are associated with poorer cognitive performances measured by 6-CIT and MMSE scales. The distinct sex/gender factor reported in this Nigerian DM2 population brings attention to the impact of short stature and poor education on the mental health of diabetic patients in Nigeria, especially in the females. We here propose that height, an easy-to-measure parameter in most clinical settings in Nigeria, may reveal increased risk of dementia among poorly educated Nigerian diabetic females. When such simple measurement is carried out routinely in Nigeria, it may help increase detection of cognitive impairment in susceptible patients and doing so improves preventive and therapeutic interventions in the country. Public policy targeting improvements of early-life nutrition and education programs, with emphasis on the girl child, may mitigate the burden of dementia in adult diabetic females.

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onset of disease, and (J) duration of disease. Cardiovascular health: (K) systolic and diastolic pressures. Mental health: (L) mean 6-CIT scores, (M) percentage of subjects at each severity level of 6-CIT scale, (N) mean MMSE scores, and (O) percentage of subjects at each severity level of MMSE scale. Data are mean ± SEM or percentages. Factorial analysis: D, DM2; S, sex; DxS, DM2 x sex interaction effects; *Post hoc*: $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ versus all the other groups; $^{d}P < .05$, $^{dd}P < .01$, $^{ddd}P < .001$ versus control group of the same sex; $^{s}P < .05$, $^{ss}P < .01$, $^{sss}P < .001$ versus the opposite sex of the same group. $^{\#}P < .05$, $^{\#\#}P < .01$, $^{\#\#\#}P < .001$ versus male control group. (*) One-tailed Student *t*-test, $P < .05$. Abbreviations: 6-CIT, six-item Cognitive Impairment Test; BMI, body mass index; CI, cognitive impairment; DM2, type 2 diabetes mellitus; MMSE, Mini–Mental State Examination; WHR, waist-hip ratio.

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. The authors sincerely thank Dr. Faeren Dogoh for his consistent and skillful training and guidance of research assistants in the collection of data from the subjects at 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's contributions: E.K.O. and L.G.-L were responsible for the study design and data interpretation and wrote the manuscript. E.K.O. was responsible of data acquisition and cognitive measures. L.G.-L. was responsible of data analysis and illustrations. Both authors approved the final version.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2019.05.006.

RESEARCH IN CONTEXT

1. Systematic review: Literature review, using PubMed and International Diabetes Federation site, focused on crosstalk between diabetes and dementia and sociodemographic and biophysical risk factors. The search indicated dramatic rising of diabetes and risk of cognitive decline/dementia in sub-Saharan African low-to-middle–income countries, with Nigeria and women being in the eye of storm. The relevant citations are appropriately cited.
2. Interpretation: The distinct sex/gender scenario in the rising diabetes mellitus type 2 population in Nigeria warns about the impact of present findings on the hallmarks short stature and poor education on the mental health of women with diabetes mellitus type 2 in Nigeria.
3. Future directions: We propose that height, an easy-to-measure parameter in most clinical settings in Nigeria, could unveil increased risk factor for dementia among poorly educated Nigerian diabetic females. Carried out routinely in Nigeria, it will help to increase detection of cognitive impairment in susceptible patients and improve preventive and therapeutic interventions in the country.

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