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Methods: This study was cross-sectional and was carried out at the Jamot Hospital in Yaounde (Cameroon), on patients with psychotic disorders and under treatment. Parameters performed on participants were physical examination and fasting glucose. Some information on the participants, such as antipsychotic therapy, physical activity, smoking, and fruit/vegetable consumption, were collected.

Results: Among the 82 patients involved in the study and with a mean age of 32.7 ± 10.73 years, 35.4% were overweight, 18.3% were obese, and 41.1% had abdominal obesity. Women were more affected by overweight and obesity compared to men ($p < 0.05$). The prevalence of hypertension was 54.9%, and of hyperglycemia was 42.7%. Low physical activity was significantly associated with the risk of being overweight (OR=5.92; CI 1.86-18.84). Atypical antipsychotic drug use increased the risk of overweight, obesity, and hyperglycemia. Smoking was associated with the risk of hyperglycemia and hypertension.

Conclusion: This study found a high prevalence of cardio metabolic biological risk factors, associated with unhealthy lifestyles and antipsychotic medication.

Keywords: cardiometabolic biological risk factors, unhealthy lifestyle, antipsychotic drugs, psychotic disorders.

1. INTRODUCTION

Cardiovascular diseases are known as one of the most common causes of premature death and great health concerns [1]. These diseases affect

all classes of the population. However, recent studies show that they are higher in patients suffering from psychotic disorders than in the general population [2]. This high CVD rate contributes significantly to impair health status and reduces life expectancy, resulting in early death in people with psychosis [3]. From an epidemiological perspective, the increased prevalence of CVD might be associated with cardiometabolic biological risk factors such as hypertension, hyperglycemia, dyslipidemia, and obesity [4]. These metabolic abnormalities might also be influenced by psychiatric conditions and an unhealthy lifestyle characterized by a high-calorie diet high in saturated fat, tobacco and alcohol consumption, and lack of physical exercise [5,6]. However, other factors such as antipsychotic medications may also exacerbate the onset of metabolic disorders, with significant weight gain, lipid disorders, and alterations in blood glucose levels [7]. Indeed, numerous studies have shown that people with psychotic disorders and under treatment have a substantial risk of death due to CVD [8] and an increased risk of developing diabetes, hypertension, and hyperlipidemia [9]. A meta-analysis revealed a prevalence of 44% abdominal obesity, 19.5% hyperglycemia, and 39% hypertension among people with psychotic disorders worldwide [10].

In sub-Saharan Africa, the prevalence of cognitive impairment in the population was between 6.3% and 25% [11], and of dementia between 2.29% and 21.60% [12]. It suggests that the population of African countries and particularly those from Cameroon are not free from this scourge [13]. However, developing an effective control strategy requires scientific data on the cardiometabolic of cardio metabolic risk factors in patients with psychotic disorders and the determinants of their progression specific to the socio-cultural context. Thus, it is of concern that cardiovascular disease is not well described in this population and the low rate of metabolic screening. Therefore, to fill these gaps, our study aims to determine the prevalence of cardio metabolic risk factors and examine whether or not the

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presence of metabolic abnormalities is associated with antipsychotic drug use and lifestyle in this vulnerable population.

II. MATERIALS AND METHODS

a) Study design and Recruitment

A cross-sectional and descriptive study carried on throughout January 2018 in the psychiatric ward of the Jamot Hospital in Yaoundé, (Central Region of Cameroon), which is a reference hospital for psychiatry in Cameroon. Patient recruitment was based on antipsychotic drugs, the absence of mental instability, and the absence of a diabetogenic diagnosis before the start of treatment. A total of 82 patients of both sexes, aged at least 18 years and suffering from psychotic disorders, were selected.

b) Ethical Consideration

The study was approved by the National Ethics Committee for Research in Human Health of Cameroon under N°2017/0588/CEIRSH/ESS/MSP and it was authorized by the Director of Jamot Hospital, Yaoundé under the reference n°00001731/MINSANTE/SG/DHJY. Free and informed consent was obtained from each patient, or their parent or legal guardian to participate in the study. The study was carried on in strict compliance with medical ethics following the Declaration of Helsinki.

III. DATA COLLECTION

a) Questionnaire

After obtaining free and voluntary consent from the participants involved in this study, well-structured questionnaires were administered by well-trained health staff. The questionnaire was adapted from the WHO Stepwise approach for surveillance of risk factors for nutrition-related chronic disease-Instrument V2.1. Participants' information on age, sex, consumption of tobacco, alcohol, fruits, and vegetables, and the antipsychotic drugs administered were collected. Antipsychotic drugs were grouped into two types: typical antipsychotics and atypical antipsychotics. Alcohol and tobacco consumption was classified into two categories: non-drinkers and drinkers and non-smokers and smokers, respectively. The participant's consumption of carried on and vegetables was grouped based on weekly intake. From 0 to 1 time per week, was classified as irregular; ≥ 2 times/week, it was classified as regular. Based on the WHO Global Physical Activity Questionnaire (GPAQ) Analysis Guide, participants were classified as having low and high levels of physical activity by using the information related to their principal activity at work, transportation, leisure activities, and sitting.

IV. MEASUREMENTS

a) Anthropometric measurements

Participants Weight was measured to the nearest 0.1 kg using a TANITA™ personal scale. Their Height was recorded using a SECA vertical scale graduated to the nearest centimeter. Body mass index (BMI) was calculated as weight using the formula: $BMI = \text{Weight (kg)} / \text{Height}^2 \text{ (m)}$ and expressed in kg/m^2 . The waist circumference was measured using a tape on the midpoint between the lower rib margin and the iliac crest in a perpendicular plane to the long axis of the body without restrictive garments.

b) Arterial blood pressure measurements

Blood pressure was measured using an OMRON electronic radial sphygmomanometer at rest. The participant was seated in a chair with the left arm parallel to the heart. The measurement was taken at the beginning of the interview after a 10-minute rest. The values obtained on the dial of the device were used to assess the presence or absence of hypertension.

c) Biochemical Analysis

Fasting blood glucose was measured by the glucose oxidase method of Trinder [14] using a glucose meter and test strips (Gluko Plus®) directly on the participant's fingertip.

d) Diagnosis of cardiometabolic risk factors

Nutritional status has been defined according to WHO criteria as follows: overweight has been defined as a BMI between 25 and 29.9 kg/m^2 and has as a BMI $\geq 30 \text{ kg/m}^2$ [15]. Other metabolic abnormalities were diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III as follows: Abdominal obesity, determined by high waist circumference ($>102 \text{ cm}$ for men and $>88 \text{ cm}$ for women); Hyperglycemia, (fasting blood glucose $\geq 110 \text{ mg/dL}$) and Hypertension, (high blood pressure: Systolic Blood Pressure (SBP) $\geq 130 \text{ mmHg}$ and Diastolic Blood Pressure (DBP) $\geq 85 \text{ mmHg}$) [16].

e) Statistical analysis

The data was analyzed using SPSS version 25.0 for Windows. The results were showed as a mean $\pm$ standard deviation (SD) for continuous variables and as a frequency (%) for categorical variables. The Pearson chi-square test was used to compare proportions between categorical variables. The student's t-test was used to detect differences in between two groups of a continuous dependent variable. Bivariate logistic regressions were used to assess the risk of developing metabolic abnormalities. The significance level used was $p < 0.05$.

V. RESULTS

The study population included 82 patients with psychotic disorders of which 41 were women and 41

men. The clinical characteristics of the study population were presented in Table 1. The mean BMI of participants was significantly ($p<0.05$) higher in women (28.72 ± 5.56 kg/m²) than in men (23.89 ± 3.45 kg/m²). A similar observation was noticed with the waist circumference of females (96.93 ± 14.74 cm) than in males (88.54 ± 12.97

cm). At the same time, the mean height was significantly higher in men (1.72 ± 0.09 m) than in women (1.67 ± 0.10 m) ($p<0.05$). However, no significant difference was noticed between men and women considering the means of age, weight, fasting blood glucose, systolic blood pressure, and diastolic blood pressure.

Table 1: Clinical characteristics of the study population

Parameters	Population	Women	Men	P-value
Age (years)	32.70±10.73	33.07±9.67	32.32±11.81	0.752
Weight (kg)	75.82±14.38	78.83±15.88	72.80±12.16	0.057
Height (m)	1.72±0.11	1.67±0.10	1.72±0.09	0.0001*
BMI (kg/m ²)	26.30±5.20	28.72±5.56	23.89±3.45	0.0001*
WC (cm)	92.73±14.43	96.93±14.74	88.54±12.97	0.008*
Blood glucose (mg/dL)	108.26±23.93	104.83±22.84	111.68±24.78	0.197
SBP (mmHg)	132.51±25.19	131.71±20.84	133.32±29.13	0.774
DBP (mmHg)	80.41±14.66	79.66±16.09	81.17±13.22	0.643

BMI=body mass index, WC=Waist circumference, SBP=systolic blood pressure, DBP=diastolic blood pressure, *=significant difference.

As shown in Table 2, the prevalence of overweight and obesity was significantly higher in women (48.8% and 29.3%) than in men (22% and 7.3%, respectively). Furthermore, the prevalence of hyperglycemia was significantly higher in men (53.7%) than in women (31.7%). In the general population, 35.4%

(n=29) of participants were overweight ($25\leq$ BMI $\leq$ 29kg/m²), 18.3% (n=15) were obese (BMI $\geq$ 30kg/m²) and 42.7% (n=35) had hyperglycemia. However, high blood pressure was more prevalent in the general population 54.9% (n=45), with systolic hypertension predominating 48.8% (n=40).

Table 2: Prevalence of cardiometabolic biological risk factors in the population

Biological factors	Population %(n)	Women %(n)	Men %(n)	P-value
Overweight($25\leq$ BMI $\leq$ 29kg/m ²)	35.4(29)	48.8(20)	22.0(9)	0.0001*
Obesity(BMI $\geq$ 30kg/m ²)	18.3(15)	29.3(12)	7.3(3)	0.0001*
Abdominal obesity	41.5(34)	36.6(15)	46.3(19)	0.370
Hyperglycemia	42.7(35)	31.7(13)	53.7(22)	0.044*
Systolic hypertension	48.8(40)	51.2(21)	46.3(19)	0.659
Diastolic hypertension	46.3(38)	41.5(17)	51.2(21)	0.376
Hypertension	54.9(45)	53.7(22)	56.1(23)	0.824

The majority of the study population was sedentary (63.4%) and women were less active than men (82.9% vs. 43.9%) (Table 3). The prevalence of Tobacco and alcohol consumption was 39% and 58.5%, respectively in the general population and the highest

consumption scores were recorded with men 48.8% and 63.4% for tobacco and alcohol, respectively. 50% of the participants had an irregular consumption of fruit/legumes. This irregular consumption was more pronounced among women (51.2%).

Table 3: Prevalence of unhealthy lifestyle factors in the population

Factors of unhealthy lifestyle	Population %(n)	Women %(n)	Men %(n)	P-value
Consumption of tobacco	39.0(32)	29.3(12)	48.8(20)	0.070
Consumption of alcohol	58.5(48)	53.7(22)	63.4(26)	0.370
Irregular consumption of fruit/vegetable	50.0(41)	51.2(21)	48.8(20)	0.825
Low level of physical activity	63.4(52)	82.9(34)	43.9(18)	0.0001*

Table 4 shows that participants under atypical antipsychotic medication were more affected by

overweight (46.4%), obesity (28.6%), and hyperglycemia (57.1%) regardless of gender. Patients under typical

antipsychotic medication were more significantly (66.7%). Also, gender was an significant factor in each ($p < 0.05$) affected by systolic hypertension (61.1%), category. diastolic hypertension (59.3%), and high blood pressure

Table 4: Type of antipsychotic medication and prevalence of cardiometabolic biological risk factors in the study population

Biological risk factors	Typical antipsychotic				atypical antipsychotic				P-value t*a
	Population % (n)	Women % (n)	Men % (n)	P-value	Population % (n)	Women % (n)	Men % (n)	P-value	
Overweight ($25 \leq \text{BMI} \leq 29 \text{ kg/m}^2$)	29.6(16)	37.5(9)	23.3(7)	0.013*	46.4(13)	64.7(11)	18.2(2)	0.001*	0.017*
Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$)	13.0(7)	25(6)	3.3(1)	0.013*	28.6(8)	35.3(6)	18.2(2)	0.001*	0.005*
Abdominal obesity	42.6(23)	37.5(9)	46.7(14)	0.498	39.3(11)	35.3(6)	45.5(5)	0.591	0.773
Hyperglycemia	35.2(19)	16.7(4)	50.0(15)	0.011*	57.1(16)	52.9(9)	63.6(7)	0.576	0.057
Systolic hypertension	61.1(33)	66.7(16)	56.7(17)	0.454	25(7)	29.4(5)	18.2(2)	0.503	0.002*
Diastolic hypertension	59.3(32)	58.3(14)	60.0(18)	0.901	21.4(6)	17.6(3)	27.3(3)	0.544	0.001*
Hypertension	66.7(36)	66.7(16)	66.7(20)	1.000	32.1(9)	35.3(6)	27.3(3)	0.657	0.003*

P-value t*a: p-value observed for comparison between patients on typical and atypical antipsychotics

Table 5 shows that participants on typical antipsychotics consumed significantly more alcohol (68.5%) than those on atypical antipsychotics (39.3%). Moreover, regardless of antipsychotic treatment, women were significantly less active than men ($p < 0.05$).

Table 5: Type of antipsychotic and prevalence of unhealthy lifestyle factors in the study population

Factors of unhealthy lifestyle	Typical antipsychotic				Atypical antipsychotic				P-value t*a
	Population % (n)	Women % (n)	Men % (n)	P-value	Population % (n)	Women % (n)	Men % (n)	P-value	
Consumption of tobacco	42.6(23)	29.2(7)	53.3(16)	0.074	32.1(9)	29.4(5)	36.4(4)	0.700	0.358
Consumption of alcohol	68.5(37)	66.7(16)	70.0(21)	0.793	39.3(11)	35.3(6)	45.5(5)	0.591	0.011*
Irregular consumption of fruits/vegetable	51.9(28)	54.2(13)	43.3(13)	0.429	46.4(13)	47.1(8)	63.6(7)	0.390	0.641
Low level of physical activity	59.3(32)	79.2(19)	43.3(13)	0.008*	71.4(20)	88.2(15)	45.5(5)	0.014*	0.278

P-value t*a: p-value observed for comparison between patients on typical and atypical antipsychotics

Table 6 presents the occurrence risk of cardio metabolic biological risk factors associated with using a type of antipsychotic drug. The use of the atypical antipsychotic drug increased the risk of overweight (OR=3.59; 95% CI: 1.19-10.80), obesity (OR=5.06; 95% CI: 1.37-18.65), and hyperglycemia (OR=2.45; 95% CI: 0.96-6.24).

Tableau 6: Bivariate logistic regression showing the association of cardiometabolic biological risk factors and the use of antipsychotic drugs.

Biological risk factors	Treatment with antipsychotics		
	Typical reference	Atypical OR (95%)	P-value
Overweight($25 \leq \text{BMI} \leq 29 \text{kg/m}^2$)	1	3.59 (1.19-10.80)	0.022*
Obesity($\text{BMI} \geq 30 \text{kg/m}^2$)	1	5.06 (1.37-18.65)	0.015*
Abdominal obesity	1	0.87 (0.34-2.21)	0.872
Hyperglycemia	1	2.45 (0.96-6.24)	0.059
Systolic hypertension	1	0.21 (0.07-0.58)	0.003*
Diastolic hypertension	1	0.18 (0.06-0.53)	0.002*
Hypertension	1	0.23 (0.08-0.62)	0.004*

The influence of an unhealthy lifestyle on the risk of developing metabolic pathologies is illustrated in Table 7. Globally, tobacco consumption increased the risk of developing hyperglycemia (OR=2.01; 95% CI: 0.81-4.97); diastolic hypertension (OR=1.92; 95% CI: 0.78-4.73) and hypertension (OR=1.34; 95% CI: 0.55-3.31). A sedentary lifestyle increased the risk of being overweight (OR=5.92; 95% CI: 1.86-18.84) and obese (OR=3.39; 95% CI: 0.91-12.60). However, the consumption of alcohol and the irregular consumption of fruit/vegetable does not influence the occurrence of cardio metabolic biological risk factors in the study population.

Table 7: Bivariate logistic regression model showing the association of cardiometabolic biological risk factors and the unhealthy lifestyle

Cardiometabolic biological risk factors	Tobacco consumption			Alcohol consumption			Consumption of fruit/vegetable			Level of physical activity		
	No ref	Yes OR (95%)	P- value	No ref	Drinkers OR (95%)	P- value	Regular ref	Irregular OR (95%)	P- value	Active ref	Inactive OR (95%)	P- value
Overweight ($25 \leq \text{BMI} \leq 29 \text{kg/m}^2$)	1	0.61 (0.22-1.63)	0.326	1	0.64 (0.23-1.72)	0.378	1	0.84 (0.31-2.21)	0.724	1	5.92 (1.86-18.84)	0.003*
Obesity(BMI $\geq 30 \text{kg/m}^2$)	1	0.15 (0.03-0.77)	0.023*	1	0.45 (0.13-1.53)	0.204	1	0.78 (0.23-2.60)	0.696	1	3.39 (0.91-12.60)	0.067
Abdominal obesity	1	0.61 (0.24-1.53)	0.299	1	0.67 (0.27-1.64)	0.388	1	1.00 (0.41-2.40)	1.000	1	1.10 (0.44-2.74)	0.838
Hyperglycemia	1	2.01 (0.81-4.97)	0.128	1	0.73 (0.30-1.79)	0.501	1	0.73 (0.30-1.78)	0.503	1	0.77 (0.31-1.91)	0.580
Systolic hypertension	1	1.08 (0.44-2.63)	0.860	1	0.92 (0.38-2.21)	0.853	1	1.00 (0.42-2.37)	1.000	1	0.60 (0.24-1.50)	0.279
Diastolic hypertension	1	1.92 (0.78-4.73)	0.152	1	0.95 (0.39-2.29)	0.913	1	0.67 (0.28-1.61)	0.376	1	0.79 (0.32-1.95)	0.614
Hypertension	1	1.34 (0.55-3.31)	0.513	1	0.93 (0.38-2.25)	0.878	1	0.90 (0.38-2.16)	0.824	1	0.72 (0.29-1.79)	0.480

ref=reference

VI. DISCUSSION

Cardiovascular diseases are known as one of the most common causes of premature death and great health concerns [1]. These cardiovascular diseases are due to a propensity for cardiometabolic risk factors. These can be exacerbated by a state of psychosis and a poor lifestyle [5,6]. This study aimed to determine the prevalence of cardiometabolic risk factors and examine whether the presence of metabolic abnormalities is associated with antipsychotic drug use or lifestyle in this vulnerable population.

The state of cardiometabolic risk factors in Cameroonian patients with psychotic disorders revealed that low physical activity was predominant in this population (63.4%). It could be due to the side effect of antipsychotic drugs, which included fatigue. Psychiatric symptoms and the severity of mental illness could also explain the participants' inactivity [17]. High levels of physical inactivity in mentally ill patients and under treatment were also observed by Nyboe and Lund [18]. Independently of the sensitization campaign on the side effects of tobacco and alcohol, it was found that 58.5 % of the subjects consumed alcohol and 39 % were smokers. The reason behind this could be the westernization of lifestyle habits and especially the popularisation of these products. However, the beneficial effect of the nicotine contained in tobacco on cognition and mood could also explain the fact that these persons with psychotic disorders often smoked tobacco [19]. An increase in tobacco and alcohol consumption among patients suffering from psychotic disorders than the general population was highlighted by Hartz et al. [20]. Half of the participants in this study had a low intake of fruits and vegetables. Indeed, low fruit and vegetable consumption associated with tobacco and alcohol consumption have been reported in people with psychosis [21]. Likewise, a low-fiber diet was found in these patients [22]. In general, low fruit and vegetable consumption accompanied by unhealthy behaviors have been observed in patients undergoing treatment with typical and atypical antipsychotic drugs. It would be attributed much more to the mental illness itself than to the use of antipsychotic medication.

Regarding cardiometabolic biological risk factors, 35.4% of patients were overweight, and 18.3% were obese. Overall, among the overweight or obese participants, the majority were women. An observation of the physical activity data also showed that women were more inactive. Therefore, women's physical inactivity may account for their high prevalence of obesity. Sultani et al. [23] also observed a significant association between low physical activity and obesity in people with psychotic illnesses. In this study, the irregular consumption of fruits and vegetables (less than once a week) by 50% of the participants could also justify the high prevalence of obesity. Indeed, high

consumption of fruit will provide the body with dietary fiber which will increase satiety leading to a reduction in total energy intake and prevents weight gain [24]. On the other hand, the overweight observed in patients under antipsychotic drugs is probably secondary to an increase in food consumption due to the stimulant effect of the drugs. The action of antipsychotic drugs is believed to involve a blockade of dopamine and monoamine receptors leading to a potential increase in appetite with weight gain as an inference [25]. Sicras-Mainar et al. [26] showed that body mass index was significantly elevated in patients on antipsychotic medication and that obesity was associated with antipsychotic medication use. However, our results revealed that overweight was more prevalent among participants on atypical antipsychotic medication. This might be explained by the concomitant blocking of dopamine and serotonin receptors by atypical antipsychotics, which contribute to an increased risk of overweight and obesity, as opposed to typical antipsychotics that are more specific to dopamine receptors [27].

The occurrence of overweight due to the combined effect of low physical activity, antipsychotic medication, and a diet low in fruits and vegetables could also explain the presence of abdominal obesity in the participants via adipose tissue dysfunction leading to fat redistribution preferentially in the abdomen [28]. However, abdominal obesity was more prevalent in men (46.3%) than to women (36.6%) regardless of the type of antipsychotic drug administered. This could be explained by the heavy consumption of tobacco (48.8%) and alcohol (63.4%) in men. Nicotine is thought to affect fat distribution through its anti-estrogenic effect, which favors android-type fat distribution, and through the increase in stress hormones such as cortisol [29]. Also, alcohol consumption inhibits fat oxidation, thus promoting the accumulation and retention of lipids in visceral adipose tissue [30].

Participants were also affected by hyperglycemia (42.7%). Smoking in study patients could explain this abnormality in carbohydrate metabolism by inducing oxidative stress due to an increase in reactive oxygen species, be the cause of insulin resistance leading to the deregulation of blood glucose homeostasis [31]. It supports our results, which showed that tobacco consumption increased the risk of developing hyperglycemia by 2.01 times. However, men were more exposed to hyperglycemia (53.7%) than to women (31.7%). Smoking associated with the presence of more abdominal fat accumulation prevalent in men would be the cause. Indeed, it has been shown that abdominal obesity induces an excess of circulating free fatty acid, which is directly deleterious to insulin signaling, thus inhibiting GLUT4 translocation, resulting in the development of hyperglycemia [32] (Samaan et al., 2008). Besides, taking antipsychotics may indirectly

contribute to hyperglycemia through weight gain since excess body fat is known to be a risk factor for many metabolic disturbances such as hyperglycemia [33]. Indeed, Lorraine et al. [34] showed that patients under antipsychotic treatment were associated with a high risk of hyperglycemia.

Hypertension was the most prevalent cardiometabolic biological risk factor in this population (54.9%). This result could be explained by tobacco consumption, which exerts a persistent effect of pressure and tachycardia, by a mechanism that involves stimulation of the sympathetic nervous system with a consequent increase in blood pressure [35]. The high prevalence of hypertension could also be explained by the use of antipsychotic medication. Although the mechanisms by which antipsychotic drugs cause hypertension is not yet well understood, several studies have shown that patients on antipsychotic drugs (aripiprazole) have developed hypertension [36].

VII. CONCLUSION

This study revealed that Cameroonians with psychotic disorders are prone to cardiometabolic biological risk factors, including overweight, obesity, abdominal obesity, hypertension, and hyperglycemia. However, an unhealthy lifestyle characterized by low levels of physical activity and tobacco use, combined with antipsychotic medication, particularly atypical antipsychotics, contribute significantly to the occurrence of cardiometabolic biological risk factors. In light of these observations, it is important for healthcare providers to be aware of the potential cardiovascular adverse effects of antipsychotics and bad lifestyle behaviors, and to monitor and address Cardiometabolic biological risk factors in patients with psychosis. This study suggests that important steps should be taken by the government to reduce the morbidity and mortality of patients suffering from psychosis, and therefore consider the findings of this study to better improve the care and management of people suffering from psychosis in Cameroon. These measures should take into consideration the specific needs according to the socio-cultural context

Authors' Contributions

OYMB, KOJP, RHH designed and conducted the study; RHH collected the data; MWN, RBTT, and AACN conducted the statistical analysis of the data; MWN, RBTT, RHH, and CMSB wrote the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this document.

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