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Original Research

B-Mode Ultrasound Grading of Cryptogenic Steatotic Liver Disease and Association with the Level of Sun Exposure in Zaria, Nigeria: A Case-Control Study.

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Abstract

Background: Cryptogenic Steatotic Liver Disease (CSLD) is a novel subject where the liver has significant steatosis but without a known cause or abnormal cardiometabolic risk factors. Its aetiology and associations with sunlight exposure remain underexplored, particularly in Nigeria. CSLD is a growing public health concern in Nigeria, characterized by its potential progression to severe liver complications such as cirrhosis and liver cancer, posing significant health risks. This study aimed to determine the association between CSLD and the level of sun exposure.
Methodology: This case-control study involved 181 healthy subjects with CSLD and an equal number of normal subjects without CSLD as controls. This made for a total number of 362 subjects. They were recruited into the study consecutively as they emerged after clinical, laboratory, and imaging screenings. A liver ultrasound scan was done using a 3.5MHz frequency transducer to screen for the steatotic liver. The severity of liver steatosis was evaluated by ultrasound bright liver scores (BLS). A daily sun exposure score based on our local pattern was calculated using the information from the administered questionnaire. The data were analyzed with GraphPad Prism software version 6.
Results: the median (IQR) age of CSLD and control groups were 44.0 (28.5 - 54.0) and 44.0 (30.0 - 55.0) years. Wilcoxon matched pairs signed rank comparison test showed no significant difference in the ages of the two study groups (p = 0.5578), indicating age matching of the study participants. There was a significant association (χ^2 = 59.03, df = 18, p< 0.0001) between age and development of CSLD. One hundred and eighty-one study subjects with CSLD comprised 83 (45.8%) males and 98 (54.1%) females.
The median (IQR) values of the control group's sun exposure score differed significantly from those of the CSLD groups (p = 0.0001) for all categories (mild, moderate, severe steatosis). A multivariate logistic regression analysis model, weighted by years of age and sex, revealed that low sunlight exposure is a significant independent risk factor.
Conclusion: The study shows that limited sun exposure is significantly associated with developing CSLD among Nigerians in Zaria. There is also a significant independent risk factor.

Keywords: B-Mode Ultrasound; Grading; Cryptogenic Steatotic Liver Disease; Sun Exposure.

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Introduction

The accumulation of adipocytes greater than 5% of total liver weight constitutes hepatic steatosis [1]. In 2023, a new nomenclature of "metabolic associated steatotic liver disease" (MASLD) has emerged by incorporating cardio-metabolic criteria to redefine "non-alcoholic fatty liver disease" (NAFLD). Among steatotic liver disease (SLD), those having no known causes and without any one of cardio-metabolic criteria are deemed to have "cryptogenic steatotic liver disease" [2]. CSLD is a novel subject with an unknown cause, therefore, the world is waiting for precise identification of its causal agents by future research [2]. CSLD represents a significant public health issue globally [2].

Unlike other liver diseases with well-defined aetiologies (such as viral hepatitis or alcohol-related liver disease), CSLD poses a diagnostic challenge due to its elusive origin[2]. As a significant component of steatotic liver disease (SLD), CSLD has become increasingly prevalent worldwide[2]. The rising incidence of CSLD may likely be associated with changing lifestyles, urbanisation, and shifts in dietary patterns, making it a critical area of study [2]. Despite the growing burden of CSLD, limited research explicitly addresses its prevalence, risk factors, and optimal diagnostic approaches in the Nigerian population; understanding how lifestyle such as sun exposure can influence CSLD could lead to more effective prevention and management strategies tailored to local needs.

Ultrasound imaging is a non-invasive, cost-effective method for diagnosing liver steatosis, but its grading and interpretation can vary based on multiple factors [3]. There needs to be more data on the effect of lifestyle factors such as level of sun exposure on CSLD development and progression worldwide. The relationship between this factor and the development of CSLD and its severity as determined by ultrasound grading is yet to be thoroughly explored in this context. CSLD may progress to metabolic dysfunction associated with steatohepatitis (MASH) and even to frank liver fibrosis and hepatocellular carcinoma [2]. It is expected in the future to be the primary indication for liver transplant from these complications [2].

The index study aimed to document probably for the first time among Nigerian adults, the association of neglected risk and modifiable factors such as sun exposure with the development of CSLD.

Methodology

The study was a case-control type carried out in the tertiary institutions in Zaria and the environment between February 1 to September 30, 2024. A case-control study was the best option for this study to establish the association between sleep deprivation and CSLD.

The minimum sample size was calculated using the formula for a binary exposure case-control study by Sainani [4]. Therefore, 181 normal subjects with CSLD and an equivalent number of sex- and age-matched controls (normal subjects without CSLD) were studied, making for a total number of 362 subjects who were recruited into the study consecutively as they emerged after the clinical, laboratory and imaging screenings. Three thousand five hundred participants were screened clinically after which 338 participants found unfit clinically were excluded from the study, and 3162 who were apparently healthy went through a series of laboratory tests and liver ultrasound scans. At the end of the laboratory investigations and ultrasound scan, only 362 participants who met the inclusion criteria were retained in the study, while 2800 who failed to meet the inclusion criteria were excluded from the study. Subsequently, only healthy subjects with steatotic liver disease (SLD) on ultrasound formed the subjects' group, and those without CSLD served as controls.

Study Population: The study was carried out in a group of adults (18-70 years), non-alcoholic and otherwise healthy subjects with ultrasound-detected steatotic liver, and another (control) group of healthy subjects without ultrasound-detected steatotic liver. The participants were recruited from those who receive routine medical check-ups in the General Out-patient/Family Medicine Clinic of ABUTH, Zaria, and medical centres of Ahmadu Bello University at Samaru and Kongo campuses.

Inclusion Criteria: Healthy subjects (18-70 years) with ultrasound-detected steatotic liver (subjects) and those without steatotic liver (controls) were recruited at the tertiary institutions in Zaria and environs.

Exclusion Criteria: Adult healthy subjects who do not consent to the study. All patients with signs of congestive cardiac failure, previous myocardial infarction, idiopathic cardiomyopathy, pericarditis, and malignancies, severe chronic liver disease, apart from the lone finding of fatty liver on ultrasound, alanine transaminase (ALT) > 30 IU/L in men and ALT > 19 IU/L in women; acute or chronic viral hepatitis which will be ruled out via laboratory screening tests, diabetes mellitus (fasting glucose ≥ 126 mg/dl or HbA1c ≥ 6.5%) or patients on anti-diabetic drugs, particularly metformin**,** overweight (body mass index [BMI] ≥ 25) and underweight (mal-nourished) with BMI < 18.5, acute or chronic rheumatic, autoimmune, or infectious disease, alcohol consumption or drug abuse, renal insufficiency, i.e., glomerular filtration rate < 60 mL/min per 1.73 m^2**,** Human immunodeficiency virus (HIV) infection, pregnancy**,** systemic hypertension**,** Homa-IR > 1.0 Unit, waist circumference (WC) > 94 cm and > 80 cm in males and females respectively. According to these exclusion criteria 1800 further subjects, potentially but only partially eligible, were excluded by this study.

Ethical Considerations: The study received ethical approval from the Human Research Ethics Committee (HREC) of the Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, with reference No: ABUTH/HREC/CL/05. All participants provided signed informed consent before recruitment into the study. The researcher and trained assistants completed the proforma.

Abdominal ultrasound scan: The abdominal ultrasound scan was performed using a real-time ultrasound scanner (Mindray diagnostic ultrasound systems, Model DC-3, 2010-12, Nanshan, Shenzen, PR China) fitted with a curvilinear array transducer with a frequency range of 3.5MHz. An experienced radiologist carried out the procedure with 20 years in the liver and gastrointestinal radiology sub-specialty. He was blinded to the laboratory and clinical details of the participants at the time of the procedure to avoid bias. In deep inspiration, the liver was examined in the supine, correct anterior oblique, and left lateral positions. The intercostal view was also employed for additional information. The presence of fat (steatosis) was recorded as a marked increase in hepatic echogenicity, poor penetration of the posterior segment of the right lobe of the liver, and poor or non-visualisation of the hepatic vessels and diaphragm. Hepatic fat quantification, i.e., ultrasound bright liver score (BLS), was graded into four levels (0–3) [5].

Grade 0: normal.
Grade 1: mild steatosis, which manifests as a significant diffuse increase in liver echogenicity compared to the kidney with normal visualisation of the intrahepatic vessel walls and diaphragm.
Grade 2: moderate steatosis, which manifests as a diffuse increase in liver echogenicity compared to the kidney with poor visualisation of intrahepatic vessel walls.
Grade 3: manifests as a severe diffuse increase in liver echogenicity with poor visualisation of deep liver parenchyma and diaphragm.

The ultrasound BLS has been previously validated by US-guided fine needle aspiration biopsy using 20 Gauge Menghini's needles [6].

Sun Exposure Score: Participants completed sun exposure questionnaires that were based on time of exposure to the sun (Score 0 = < 5 minutes; score1 = 5–30 minutes; and score 2 = > 30 minutes) and skin exposure to the sun (score1 = face and hands uncovered; score 2 = arms uncovered; score 3 = legs uncovered; score 4 = "bathing suit") for each day in the previous week (Table I). This sun exposure questionnaire has been validated by Sham *et al*[7] and Hanwell *et al*[8]. A daily sun exposure score was calculated based on the product of the time exposed to sun and skin exposed to sun scores (minimum score = 0, maximum score = 8), and a weekly sun exposure score was calculated by taking the sum of each day's exposure scores. A minimum score of 0 corresponded to < 5 minutes outdoors in the sun for each day in each week, and a maximum score of 56 corresponded to > 30 minutes in a bathing suit outdoors in the sun for 7 days a week (Table I) [7].

Table 1: Sun exposure scores [7]

	Time Exposed to Sun			**Skin Exposed to the Sun**			
Day	**<5 min**	**5-30 min**	**>30 min**	**Face and hands**	**Arms uncovered**	**Legs Uncovered**	**Bathing Suit**
Mon	0	1	2	1	2	3	4
Tues	0	1	2	1	2	3	4
Wed	0	1	2	1	2	3	4
Thurs	0	1	2	1	2	3	4
Fri	0	1	2	1	2	3	4
Sat	0	1	2	1	2	3	4
Sun	0	1	2	1	2	3	4

Statistical Analysis: Data was analysed with GraphPad Prism software version 6, manufactured by GraphPad Software, LLC, 225 Franklin Street, Floor 26, Boston, MA 02110, USA. The data were summarised using median (and interquartile range [IQR]) for skewed data and mean (±SD) for normally distributed data. Categorical variables were presented as frequencies. A comparison of significant differences between the control group and the three different categories of subjects with CSLD, mild, moderate, and severe, was conducted using Kruskal-Wallis with Dunn's post-hoc analysis for skewed variables. The Chi-square test for independence was used to determine relationships between variables. A p-value ≤ 0.05 was considered statistically significant. A multivariate logistic regression analysis model, weighted by years of age and sex was carried out to establish the significance of the level of sun exposure as an independent risk factor in the development of CSLD.

Results

The median (IQR) age of CSLD and control groups were 44.0 (28.5-54.0) and 44.0 (30.0-55.0) years. Wilcoxon matched pairs signed rank comparison test showed no significant difference in the ages of the two study groups (p = 0.5578), indicating age matching of the study participants. Table 2 shows the sex-matched distribution of subjects with CSLD and control subjects with an equal number of participants of the same sex in each group. The Chi-square test indicated no significant association between the sex of the participants and the development of CSLD (p = 0.9160).

Table 2: Sex-matched distribution of subjects with cryptogenic steatotic liver disease (CSLD) and control subjects in Zaria, Nigeria.

Data analyzed	CSLD	Control	Total
Female	98	98	196
Male	83	83	166
Total	181	181	362

Chi-square (with Yates' correction) = 0.011, df = 1; OR = 1.000 (95% CI: 0.6613 to 1.512); p – value = 0.9160

Sociodemographic characteristics of subjects with CSLD and control subjects: One hundred and eighty-one study subjects with CSLD were categorized according to severity into mild (n = 89), moderate (n = 78), and severe CSLD (n = 14). They were studied alongside a healthy control group (n = 181). Of the subjects with CSLD, a total of 98 (54.1%), females constituted 44 (24.3%) with mild, 46 (25.4%) with moderate and 8 (4.4%) with severe CSLD. The 83 (45.9%) males with CSLD constituted 45 (24.9%), 32 (17.7%), and 6 (3.3%) with mild, moderate, and severe CSLD respectively. The Chi-square test for independence showed no significant association (χ^2 = 1.578, df = 3, p = 0.6645) between sex and the development of CSLD (Table 3).

Of the subjects with CSLD, those aged 20-29 years constituted 32 (17.7%) with mild, 14 (7.7%) with moderate, and 1 (0.6%) with severe CSLD; those aged 30-39 years constituted 10 (5.5%) with mild, 13 (7.2%) with moderate and 1 (0.6%) with severe CSLD; those aged 40-99 years constituted 27 (14.9%) with mild, 15 (8.3%) with moderate and 2 (1.1%) with severe CSLD; those aged 50-59 years constituted 19 (10.5%) with mild, 28 (15.5%) with moderate and 4 (2.2%) with severe CSLD; those aged 60-69 years constituted 1 (0.6%) with mild, 5 (2.8%) with moderate and 6 (3.3%) with severe CSLD; those aged 70 years constituted only 3 (1.7%) with moderate CSLD. Of the control group,41 (22.7%) were 20-29 years, 33 (18.2%) were 30-39 years, 40 (22.1%) were 40-49 years and 50-59 years each, 16 (8.8%) were 60-69 years while 11 (6.1%) were aged70 years. The Chi-square test for independence showed a significant association (χ^2 = 59.03, df = 18, p = 0.0001) between age and development of CSLD (Table 3).

Table 3: Sociodemographic characteristics of subjects with cryptogenic steatotic liver disease (CSLD) and control subjects in Zaria, Nigeria

Characteristic	**CSLD**			**Control**	**Statistics**
	Mild (n=89)	**Moderate (n=78)**	**Severe (n=14)**	**(n=181)**	
Sex (%)					
Female	44 (24.3)	46 (25.4)	8 (4.4)	98 (54.1)	χ^2=1.578, df=3, p=0.6645
Male	45 (24.9)	32 (17.7)	6 (3.3)	83 (45.9)	
Age-group (%)					
20-29	32 (16.6)	14 (7.7)	1 (0.6)	41 (17.7)	
30-39	10 (5.5)	13 (7.2)	1 (0.6)	33 (18.2)	
40-49	27 (14.9)	15 (8.3)	2 (1.1)	40 (22.1)	χ^2=59.03, df=18, p<0.0001*
50-59	19 (10.5)	28 (15.5)	4 (2.2)	40 (22.1)	
60-69	1 (0.6)	5 (2.8)	6 (3.3)	16 (8.8)	
70	0 (0.0)	3 (1.7)	0 (0.0)	11 (6.1)	

Sun exposure scores: The median (IQR) value of the sun exposure score of the control group was higher significantly when compared with the CSLD groups (p = 0.0001). In Figure 1, the Median values of the groups were compared using Kruskal Wallis with Dunn's post-hoc analysis.

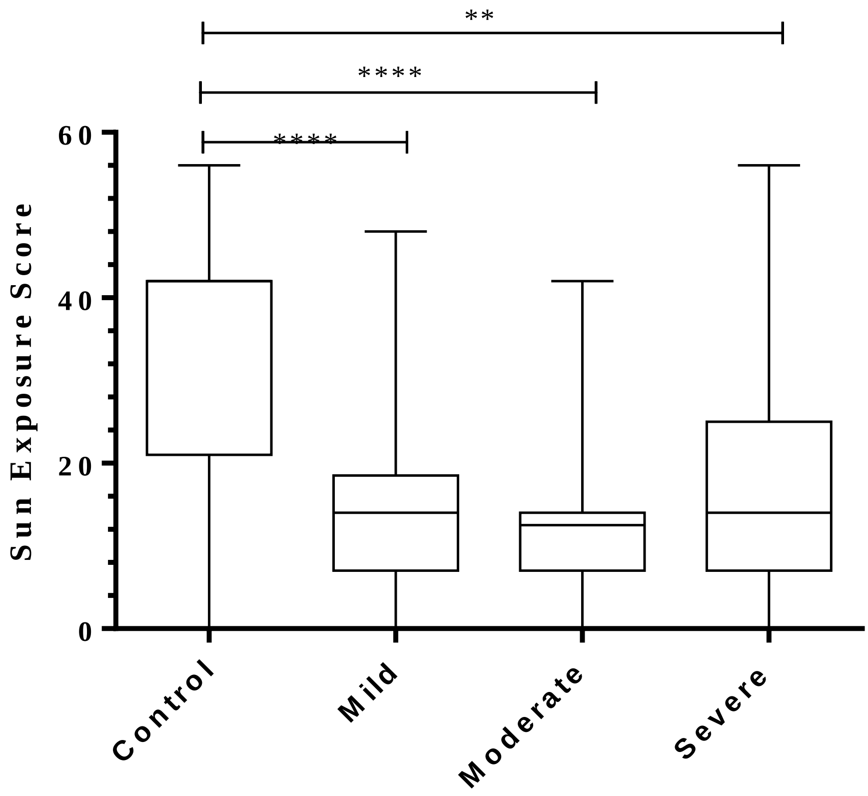

Fig. 1: Significant decrease in sun exposure as determined by Kruskal Wallis (**p<0.0001).**

Dunn's post-hoc analysis showed a significant difference between the control group and all groups of CSLD. Multivariate logistic regression analysis model, weighted by years of age and sex revealed that low sunlight exposure is a significant independent risk factor.

Discussion

The index study shows that there is no relationship between gender and the development of CSLD in the cohort which was well matched for age and sex in both CSLD and the control groups. However, there is no similar study yet after an extensive literature search on the relationship between the gender and development of CSLD. But the previous studies on the relationship between gender and the development of non-alcoholic fatty liver disease (NAFLD), show that NAFLD is significantly commoner in men than women [9,10]. The differences between both genders according to the study by Williams *et al* [9] are thought to be attributable to differences in lifestyle. A postmenopausal peak in the incidence of NAFLD observed among women by Kim *et al* [11] is thought to be due to sex steroid metabolism, which is implicated in NAFLD pathogenesis [12].

The index study shows a significant association between age and development of CSLD. However, there is no similar study yet after an extensive literature search on the relationship between the age and development of CSLD. However, similar findings have been previously established between age and development of NAFLD by Musso *et al* [13], in which the maximum number of patients was in the 3rd decade, followed by the 5th decade.

Most patients with CSLD are asymptomatic, which is also evident from the index study, as the subjects who constituted the cases were all healthy. However, malaise, fatigue, and right upper quadrant pain have been reported in a previous study on NAFLD [8].

The index study found that sun exposure scores were higher in the control group than in all the sub-groups with CSLD. As such, a shorter duration of sun exposure showed a statistically significant association with CSLD. Also, the Multivariate logistic regression analysis model, weighted by years of age and sex revealed that low sunlight exposure is a significant independent risk factor. However, no similar study has yet after an extensive literature search on the relationship between the sun exposure score and the development of CSLD. However, previous studies on NAFLD show that exposure to sunlight could be a neglected risk factor in the development of NAFLD [14,15,16]. In a report by Holick [14], vitamin D deficiency has reached pandemic proportions, with over a billion people worldwide being affected by vitamin D deficiency. The ultraviolet radiation which is derived from sunlight has both local and systemic effects [14]. Because Vit D deficiency is associated with obesity and insulin resistance, it is not surprising that vitamin D deficiency could be associated with NAFLD independent of age, gender, or levels of triglycerides or glucose [15,16]. In addition, hepatic inflammation has been linked with the pathogenesis of NAFLD, hence exposure to sunlight ultra-violet radiation (UVR) may suppress liver inflammation by the release of immune modulators Vit D and nitric oxide and thus reduce the severity of NAFLD [17].In a study among human adolescents, it was found that NAFLD patients were 1.26 times more likely to be Vit D deficient [18]. However, the therapeutic effect of vitamin D supplementation in patients with NAFLD is yet to be ascertained.

Conclusion:

The shorter duration of sun exposure is significantly associated with the development of CSLD. Also, the multivariate logistic regression analysis model, weighted by years of age and sex revealed that low sunlight exposure is a significant independent risk factor. This factor is easily modifiable and should be emphasised to reduce the burden of hepatic failure from hepatocellular carcinoma since this is the possible pathway of progression of CSLD.

Limitation and recommendation: The index study was carried out at the tertiary health facilities. More broad-based community studies with larger sample sizes in various geopolitical zones of Nigeria are recommended to validate the index findings.

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