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ABSTRACT

Background While linked to obesity and associated with an increased cardiovascular morbidity, non-alcoholic fatty liver disease (NAFLD) is an often-asymptomatic cause of chronic liver disease in children. Early detection provides opportunity for interventions to curb progression. Childhood obesity is on the rise in low/middle-income countries, but cause-specific mortality data associated with liver disease are scanty. Establishing the prevalence of NAFLD in overweight and obese Kenyan children would guide in public health policies aimed at early screening and intervention.

Objectives To investigate prevalence of NAFLD in overweight and obese children aged 6–18 years using liver ultrasonography.

Methodology This was a cross-sectional survey. After obtaining informed consent, a questionnaire was administered, and blood pressure (BP) measured. Liver ultrasonography was performed to assess fatty changes. Categorical variables were analysed using frequency and percentages. χ^2 test and multiple logistic regression model were used to determine relationship between exposure and outcome variables.

Results Prevalence of NAFLD was 26.2% (27/103, 95% CI=18.0% to 35.8%). There was no association between sex and NAFLD (OR1.13, $p=0.82$; 95% CI=0.4 to 3.2). Obese children were four times more likely to have NAFLD compared with overweight children (OR=4.52, $p=0.02$; 95% CI=1.4 to 19.0). About 40.8% ($n=41$) had elevated BP, but there was no association with NAFLD (OR=2.06; $p=0.27$; 95% CI=0.6 to 7.6). Older children (13–18 years) were more likely to have NAFLD (OR 4.42; $p=0.03$; 95% CI=1.2 to 17.9).

Conclusion Prevalence of NAFLD was high in overweight and obese school children in Nairobi. Further studies are needed to identify modifiable risk factors to arrest progression and prevent sequelae.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a progressive disease that ranges from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH). When left untreated, it evolves

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Non-alcoholic fatty liver disease (NAFLD) is commonly found in overweight and obese children. While there is a growing concern for childhood obesity in low/middle-income countries, there is scarcity of data on paediatric NAFLD in low/middle-income countries in sub-Saharan Africa.

WHAT THIS STUDY ADDS

⇒ One in every four overweight and obese children in a study population in Nairobi, Kenya, has NAFLD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study creates awareness on the burden of NAFLD and will serve as a guide for further studies to identify possible modifiable risk factors through prevention and/or early treatment to avoid long-term sequelae.

into hepatic cirrhosis and hepatocellular carcinoma.¹ NAFLD is associated with cardiovascular morbidity in children and teenagers² and is now considered the hepatic manifestation of metabolic syndrome which comprises obesity, dyslipidaemia, hypertension and insulin resistance.^{3–4} Early detection and initiation of management which is primarily targeted at weight reduction through a healthy dietary intake and increased physical activity with supplementation of vitamin E and administration of metformin in select cases has been shown to reverse the disease process.^{5–7}

According to the WHO, being overweight or obese is ranked as the fifth-leading risk factor for global mortality.⁸ This is a rising public health concern for school-going children in low/middle-income countries due to an increase in sedentary lifestyle.^{9–11} In Kenya, this has been seen mainly in children from urban areas and of high socioeconomic status.¹²

The clinical onset of NAFLD is insidious, and often asymptomatic. Liver biopsy is the gold standard for diagnosis, but it is an invasive procedure with attendant risks.¹³ Liver ultrasonography is a non-invasive screening tool and has a predictive value of 87%–94% for fat load of the liver above 30%.⁵

Establishing the prevalence of NAFLD in our population will inform needed public health messages in preventing the disease process, serve as a benchmark for long-term follow-up, and aid in decreasing associated morbidity and mortality. Identifying at-risk children and detecting cases using non-invasive screening methods is an important strategy against NAFLD.¹⁴

METHODS

Study objective

The primary objective of this study was to determine the prevalence of NAFLD in overweight and obese children aged 6–18 years seeking ambulatory health services at Aga Khan University Hospital, Nairobi, and Gertrude's Children's Hospital. The two secondary objectives were to determine whether (1) hypertension is associated with NAFLD in overweight and obese children and (2) positive family history of hypertension or diabetes mellitus is associated with NAFLD in overweight and obese children.

Study design and population

A descriptive cross-sectional study was conducted in overweight and obese school-aged children aged 6–18 years seeking outpatient services at Aga Khan University Hospital (AKUH) and Gertrude's Children Hospital (GCH) in Nairobi, Kenya, from December 2016 to April 2017.

The Fisher's formula online supplemental file 1 was used to determine the number of children required for the study, using an estimated prevalence of 15.8%¹⁵ and a 7.5% degree of precision in a two-tail test giving a minimum sample size of 103.

Selection and enrolment of subjects

Children aged between 6 and 18 years who were overweight or obese, as defined by a body mass index (BMI) greater than 1 or 2 SD above the WHO growth reference median, who attended paediatric outpatient clinics at AKUH or GCH were recruited.

Inclusion criteria included children; (1) seeking ambulatory health services at AKUH and GCH, (2) aged 6–18 years with a BMI greater than 1 SD above the WHO growth reference median and (3) whose parents provided a written informed consent to participate in the study. Children with chronic illnesses other than being overweight or obese; those with known liver, cardiac and/or renal disease; those who were on anticonvulsants, antituberculosis medication and/or antiretroviral medication and those with associated substance abuse (including alcohol), were excluded.

Sampling technique

The principal investigator conducted a half-day training session in each hospital to sensitise the triage nurses

to identify overweight and obese children meeting the inclusion criteria and on proper blood pressure (BP) measurements. Enrolment continued until the desired sample size was achieved.

Data collection

The study participants were identified using consecutive serial numbers, and no personal identification details were recorded. Informed consent (online supplemental appendix 1) was obtained from the legal guardian, and further written assent was obtained from children aged 14–18 years. The children's sociodemographic and health data were entered into a questionnaire (online supplemental appendix 2).

Anthropometric measurements were conducted in children wearing light clothing and without shoes. Height was measured to the nearest 0.1 cm with SECA, a digitally calibrated portable stadiometer. Weight was measured in an upright position to the nearest 0.1 kg with a calibrated digital TANITA scale. BMI was calculated by dividing the weight (kg) by the height in metres squared (m²).

Abdominal circumference was measured to the nearest 0.1 cm at the midpoint of the lower borders of the rib cage and iliac crest, at the end of normal expiration. The waist-to-height ratio was categorised as favourable if less than 0.5, and unfavourable if more than 0.5.

BP measurements were taken on the right arm of the participants while seated after a 15 min rest. A digital SureSigns PHILIPS BP machine was used with an appropriately sized cuff for each child, ensuring that the width of the cuff was occupying approximately 40% of the length between the shoulder tip and olecranon and that the length of the cuff's bladder was at least 80% of the mid-arm circumference.¹⁶ These results were characterised by age and gender.¹⁷

Liver ultrasonography was performed at the AKUH radiology department using a PHILIPS XMATRIX iU22 model ultrasound machine with a curvilinear probe of 5–12 MHz Sonography was done using a standardised protocol (Appendix 3).

The presence of fatty liver was assessed as a diffuse hyperechoic texture (bright liver) in comparison with the echo texture of the kidneys and graded as follows¹⁸:

1. Grade 0: Normal liver echogenicity
2. Grade 1: Fatty liver with increased echogenicity compared to the right renal cortex
3. Grade 2: Fatty liver in which the echogenic liver obscures the walls of the portal venous branches
4. Grade 3: Fatty liver in which the diaphragmatic outline is obscured

All images and reports were validated by a liver imaging expert consulting radiologist. A simple coding system was developed to link the ultrasound features to the respective participants and allowed for effective tracking of the ultrasonography results and related information.

Data analysis

Statistical analyses were performed using SPSS 11.5.

Categorical variables, that is, sex, age, presence or absence of a fatty liver on ultrasound, BMI and BP categories were analysed using median (IQR) and summarised using frequency counts and percentages. The χ^2 test was used to compare associations between various independent variables such as age, sex, BMI, BP, family history of hypertension, and family history of diabetes mellitus (DM) with fatty liver change. Clinically important variables comprised of BMI, waist to height ratio and family history of DM were included in a multiple logistic regression model adjusted for age and sex to establish

independence of association with fatty liver. Statistical significance was set at $p \leq 0.05$.

RESULTS

Study population

The study included 103 children aged 6–18 years, 42.7% (n=44) were male. There was an equal number of children aged 6–9 years and 10–12 years at 40.8% (n=42) while those aged 13–18 years were 18.4% (n=19). A number of children who were studying in private

Table 1 Baseline sociodemographic characteristics of study subjects

Sociodemographic characteristics	Fatty liver (N=27)	Non-fatty liver (N=76)	All subjects (N=103)	P value
	n (%)	n (%)	n (%)	
Sex				
Male	13 (29.5)	31 (70.5)	44 (42.7)	0.51*
Female	14 (23.7)	45 (76.3)	59 (57.3)	
Age, median (IQR)	10 (8–13)	10 (8–11)	10 (8–12)	–
Age-group (years)				
6–9	11 (26.2)	31 (73.8)	42 (40.8)	0.05†
10–12	7 (16.7)	35 (83.3)	42 (40.8)	
13–18	9 (47.4)	10 (52.6)	19 (18.4)	
School attended				
Public	5 (29.4)	12 (70.6)	17 (16.5)	0.77†
Private	22 (25.6)	64 (74.4)	86 (83.5)	
Type of school				
Day	23 (26.1)	65 (73.9)	88 (85.4)	0.97†
Boarding	4 (26.7)	11 (73.3)	15 (14.6)	
Maternal highest education level				
Secondary or less	7 (30.4)	16 (69.6)	23 (22.3)	0.84*
Dip/higher/degree	14 (25.9)	40 (74.1)	54 (52.4)	
Grad/professional degree	6 (23.1)	20 (76.9)	26 (25.2)	
Paternal highest education				
Secondary or less	4 (28.6)	10 (71.4)	14 (13.6)	
Dip/higher/degree	14 (34.1)	27 (65.9)	41 (39.8)	0.26†
Grad/professional degree	9 (18.8)	39 (81.2)	48 (46.6)	
Working mother				
Yes	19 (22.9)	64 (77.1)	83 (80.6)	0.12*
No	8 (40.0)	12 (60.0)	20 (19.4)	
Working father				
Yes	26 (26.3)	73 (73.7)	99 (96.1)	0.96†
No	1 (25.0)	3 (75.0)	4 (3.9)	
Annual HH income				
Middle	10 (22.2)	35 (77.8)	45 (43.7)	0.42*
High	17 (29.3)	41 (70.7)	58 (56.3)	

* χ^2 .

†Fisher's exact.

HH, household.

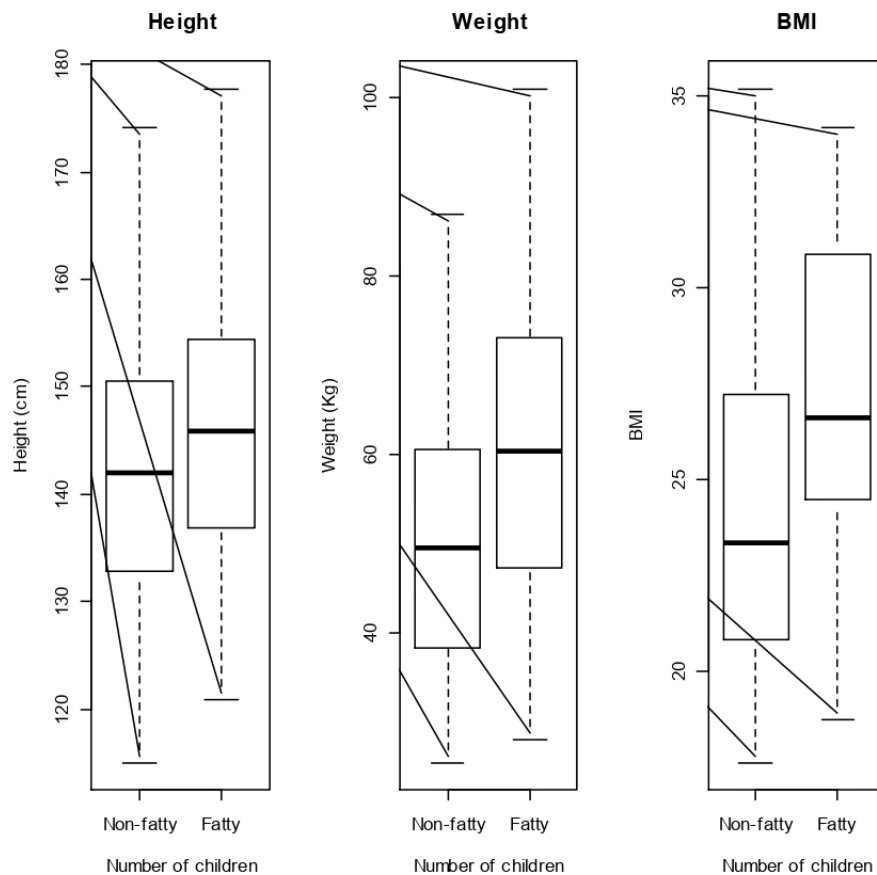


Figure 1 Box and whisker plots for height, weight and BMI with the middle thick lines showing the medians. BMI, body mass index.

schools were 83.5% (n=86) and those who were in day schools were 85.4% (n=88). Slightly more than half of the children's mothers, 52.4% (n=54), had a diploma or basic degree, while 25.2% (n=26) were graduates/professionals. Children whose fathers were graduates/professionals comprised 46.6% (n=48), 39.8% (n=41) had a diploma or basic degree. The number of working fathers was higher compared with the number of working mothers (96.1% (n=99) vs 80.6% (n=83), respectively). More than half (58 of 103) of the households had a high level of annual household income (table 1).

Estimate of prevalence of fatty liver

The overall prevalence of fatty liver in this population was 26.2% (27/103; 95% CI=18.0% to 35.6%). Twenty-four children had grade 1 fatty liver, two children had grade 2 and one child had grade 3 fatty liver changes. Fatty liver was present in 29.5% of the males compared with 23.7% of the females. Older Children of ages 13–18 years had highest prevalence at 47.4%. Children in public schools had higher prevalence of fatty liver compared with children in private schools (29.4% vs 25.6%, respectively). The prevalence of fatty liver was reduced with the maternal level of education. The prevalence was highest among children whose mothers had attained at most secondary level of education at 30.4%, 25.9% among children whose mothers had a diploma or basic degree, and 23.1% among children whose parents

were graduates or professionals. Children with mothers who were not working had a higher prevalence than children whose mothers were working. This was the reverse of the situation for children whose fathers were working. Children from families with higher annual incomes had the highest prevalence at 29.3%.

Among the sociodemographic variables, a significant association was observed only between age group and fatty liver ($p=0.05$) (table 1).

Continuous variables, weight, height and BMI were summarised using the median (IQR) for children with and without fatty liver disease (figure 1). The median (IQR) height (cm) for children with fatty liver was estimated to be 146 (137–155), median (IQR) weight (kg) was 60 (47–73) and median (IQR) BMI for the same group of children was estimated to be 27.^{19–26}

On exploring the clinical characteristics of the children, 68.0% (n=70) were obese, while 32.0% (n=33) were overweight, 86.4% (n=89) had unfavourable waist to height ratio of more than 0.5. On assessing BP readings, 60.2% of the children (n=62) had normal BP, while 40.8% (n=41) had elevated BP, of which 15.5% (n=16) had BP in the pre-hypertensive range and 24.3% (n=25) in the hypertensive range. Most of the children, 35% (n=36) were asymptomatic, 29.1% (n=30) had history of abdominal pain, 20.4% (n=21) had history of more than one abdominal symptom and 15.5% (n=16) had

Table 2 Clinical findings of the study subjects

Clinical Characteristics	Fatty liver (N=27)	Non-fatty liver (N=76)	All subjects (N=103)	P value
	n (%)	n (%)	n (%)	
BMI, median (IQR)	27 (24–31)	23 (21–27)	25 (21–28)	–
BMI category				
Overweight	4 (12.1)	29 (87.9)	33 (32.0)	0.026
Obese	23 (32.9)	47 (67.1)	70 (68.0)	
Waist to height ratio				
Favourable	0 (0.0)	14 (100.0)	14 (13.6)	0.019
Unfavourable	27 (30.3)	62 (69.7)	89 (86.4)	
Blood pressure status				
Normal	14 (22.6)	48 (77.4)	62 (60.2)	0.243
Prehypertension	7 (43.8)	9 (56.2)	16 (15.5)	
Hypertension	6 (24.0)	19 (76.0)	25 (24.3)	
Presenting complains				
None	8 (22.2)	28 (77.8)	36 (35.0)	0.841
Abdominal pain	9 (30.0)	21 (70.0)	30 (29.1)	
Multiple symptoms	5 (23.8)	16 (76.2)	21 (20.4)	
Others	5 (31.2)	11 (68.8)	16 (15.5)	
Family history of hypertension				
Yes	14 (25.0)	42 (75.0)	56 (54.4)	0.760
No	13 (27.7)	34 (72.3)	47 (45.6)	
Family history of diabetes type 2				
Yes	19 (34.5)	36 (65.5)	55 (53.4)	0.040
No	8 (16.7)	40 (83.3)	48 (46.6)	

BMI, body mass index.

unrelated complaints. The proportions of children with family history of hypertension and diabetes type 2 were 54.4% (n=56) and 53.4% (n=55), respectively.

Children who were obese had a higher prevalence of fatty liver compared with overweight children (32.9% vs 12.1%, $p=0.026$). There was no fatty liver detected in any of the children with a favourable waist to height ratio of less than 0.5; however, 30.3% of children had unfavourable waist to height ratio of more than 0.5 had fatty liver. Highest prevalence (43.8%) of fatty liver was found in children with prehypertensive BP status compared with hypertensive and normotensive status (24.0% and 22.6%, respectively). Children with a positive family history of diabetes type 2 had higher prevalence compared with those from families without (34.5% vs 16.7%), and this was associated with fatty liver ($p=0.04$) (table 2).

Descriptive findings of fatty liver and the population

There was no association between sex and fatty liver (OR=1.13; $p=0.82$; 95% CI=0.4 to 3.2). Obese children were four times more likely to have fatty liver compared with overweight children (OR=4.52; $p=0.02$; 95% CI=1.4 to 19.0). Likewise, children with fatty liver were significantly older than children of other age-groups, with four times odds of older children (13–18 years) with fatty liver

compared with younger children (6–9 years) (OR=4.42; $p=0.03$; 95% CI=1.2 to 17.9). More than a third (40.8%) (n=41) of the children had elevated BP; however, there was no association between elevated BP and fatty liver disease (OR=2.06; $p=0.27$; 95% CI=0.6 to 7.6). Finally, children from families with history of diabetes type two had three times higher odds of developing fatty liver compared with children from families without history of diabetes type 2 (OR=3.10; $p=0.04$, 95% CI=1.1 to 9.5) (table 3).

DISCUSSION

Prevalence of NAFLD in overweight and obese school going children aged 6–18 years living in Nairobi, using liver ultrasonography, was 26.2%. This is the first reported prevalence of paediatric NAFLD in sub-Saharan Africa. This prevalence is lower than that reported in similar studies conducted on overweight and obese children using liver ultrasonography. In Egypt, el-Karaksy *et al*²⁷ found a prevalence of 38% among 76 children aged 2–15 years while in India, Pawar *et al*²⁸ reported a prevalence of 62% in 100 children aged 11–15 years. A higher prevalence of 68.7% was reported in Europe by Kodhelaj *et al*²⁹ in 80 children aged 7–15 years in Albania.



Table 3 Logistic regression on factors associated with liver ultrasonography findings

Characteristic	OR	SD	P value	95% CI
Sex				
Male	Reference			
Female	1.13	0.52	0.82	0.41 to 3.24
Age categories				
6–9	Reference			
10–12	0.60	0.58	0.36	0.18 to 1.85
13–18	4.42	0.68	0.03	1.20 to 17.90
BMI Category				
Overweight	Reference			
Obese	4.52	0.66	0.02	1.36 to 19.00
BP status				
Normal	Reference			
Prehypertension	2.06	0.66	0.28	0.55 to 7.56
Hypertension	0.96	0.62	0.94	0.27 to 3.15
Family history of hypertension				
No	Reference			
Yes	0.47	0.53	0.16	0.16 to 1.31
Family history of diabetes type 2				
No	Reference			
Yes	3.10	0.55	0.04	1.10 to 9.54

BMI, body mass index; BP, blood pressure.

Different prevalence rates in different populations may be explained by postulated genetic susceptibility and epigenetic mechanisms that influence paediatric hepatic steatosis.³⁰ Moreover, the relatively lower prevalence in our study may be due to the wide age spectrum of study participants, from 6 to 18 years, compared with the study in India, which mainly looked at adolescents. NAFLD is postulated to be more prevalent in adolescents.³¹ This was confirmed in our study, where adolescents (13–18 years) were four times more likely to have fatty liver than prepubertal (6–9 years) and pubertal (10–12 years) children. The higher rate of NAFLD among adolescents may be due to an increased tendency for a hypercaloric diet and decreased physical activity² potentiated by hormonal changes that may lead to accumulation of fat in the liver.¹⁹ This has also been demonstrated in various studies in Egypt, Germany and the USA, where the prevalence of NAFLD increased with age.^{15 20 29}

In this study, children who were obese had a fourfold higher likelihood of having NAFLD than overweight children. Obesity predisposes to steatosis by initiating the primary insult to the liver via increased substrate delivery of free fatty acids within the hepatocytes, leading to increased lipogenesis and impaired fatty acid metabolism.²¹ A higher likelihood of NAFLD in obese

children than in overweight and normal-weight children has been reported in other population studies.^{22 23 31} Obesity also leads to the expansion of adipose tissue, particularly visceral fat, which leads to a secondary insult to the liver in NAFLD, with the release of proinflammatory molecules.²⁴ Expansion of adipose tissue is vaguely assessed by a waist-to-height ratio, being favourable if less than 0.5, and unfavourable if more than 0.5.^{25 26} This was demonstrated in our study which none of the children with a favourable ratio had NAFLD, whereas 30.3% of the children with NAFLD had an unfavourable ratio.

Standard weight reduction regimen with concomitant antioxidant therapy with vitamin E has been shown to significantly improve hepatocellular ballooning on histology in a subgroup of children with NASH leading to a reduction in the NAFLD Activity Score, a histological scoring system used in clinical trials to diagnose NASH.⁶ Furthermore, in a randomised control trial involving 119 children diagnosed with NAFLD using liver ultrasonography, Arani *et al* found that having controlled for diet and weight loss programme, there was reversal of fatty changes on institution of vitamin E or metformin.⁷

No significant sex differences were observed in this study. This is a secondary analysis of the findings. Unfortunately, this study was powered based on the main objective of establishing the prevalence of NAFLD and not by assessing the factors associated with the disease process. Some studies have reported that NAFLD is more common in boys than in girls^{15 31 32}; however, no significant difference was noted among Turkish and Iranian children.^{25 31}

NAFLD is associated with cardiovascular morbidity in both children and adolescents.² BP readings were used as surrogate markers for cardiovascular disease in this study. Overall, 40.8% of children had high BP readings, of which 15.5% had prehypertensive readings and 25.3% had hypertensive readings. No significant relationship was established between NAFLD and high BP readings. This could be because the study was not adequately powered to assess the association between BP and NAFLD. However, this study revealed that more than one-third of the children had high BP. This could be attributed to white-coat hypertension, defined by an abnormally high BP reading due to anxiety in the presence of a healthcare provider.¹⁶ Moreover, this was a one-off BP reading that could not be used to fully classify a child as hypertensive. Nevertheless, these findings provide insight into the possible cardiovascular morbidity in these children. Further studies and follow-up of these children are needed to fully establish this correlation, as has been positively reported in Germany³¹ India.²⁸

In our population, children with a positive family history of DM were three times more likely to have NAFLD than those without DM. Family history of obesity, hypertension and DM type 2 has been associated with NAFLD, implying a genetic predisposition to the disease process.^{3 33} Both fat accumulation in the liver and insulin resistance, a precursor of DM type 2, are interplay

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