

## Research

# Faster rehabilitation weight gain is associated with liver fat in adult survivors of childhood severe acute malnutrition

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## Background

Nutritional rehabilitation during severe acute malnutrition (SAM) aims to quickly restore a healthy body weight, but rapid weight gain has been associated with later cardiovascular risk. We hypothesized that faster weight gain during SAM rehabilitation and post-hospitalization is associated with liver fat in adult survivors.

## Method

Jamaican adult survivors of childhood SAM underwent abdominal CT scan to estimate liver fat as mean liver attenuation (MLA) and liver spleen ratio (L/S). Birth weight (BW) and anthropometry measured during, and post-hospitalization were abstracted from admission records.

## Results

We studied 42 marasmus survivors (MRs) and 40 kwashiorkor survivors (KWs). MRs had a lower mean BW (SD) 2.5 (0.8) vs 3.0 (0.7) kg;  $p=0.01$  and were more wasted ( $p<0.001$ ) and stunted ( $p=0.03$ ) than KWs on admission to hospital. MRs and KWs had similar rates of rehabilitation weight gain, which was inversely associated with MLA among all survivors of SM ( $r=-0.246$ ,  $p=0.029$ ), but only in MRs when assessed by diagnosis ( $r=-0.449$ ,  $p=0.004$ ). The association between rehabilitation weight gain and adult liver fat in MRs was not altered by BW, admission wasting or stunting. In KWs, post-hospitalization height gain was inversely associated with MLA (difference = -0.64, 95%CI: -0.64 to -0.13;  $p=0.006$ ).

## Conclusions

Faster rehabilitation weight gain is associated with liver fat in adult survivors of childhood severe acute malnutrition. The finding that BW did not influence these outcomes may reflect the timing of the nutritional insult in utero. Target weight gain during nutritional rehabilitation may need to be lowered to optimize long-term outcomes in these children.

## INTRODUCTION

Early life exposure to severe acute malnutrition has been reported to be associated with later non-communicable diseases (Mwene-Batu et al. 2021; Grey et al. 2021) possibly

including non-alcoholic fatty liver disease (NAFLD). Indeed, famine exposure in early life has been shown to have a significant association with the risk of NAFLD in adult women (Zheng et al. 2017). Factors that might influence liver fat accumulation in persons fully recovered from se-

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vere acute malnutrition are birth weight (BW), the degree of wasting and/or stunting on admission and the rate of weight gain during nutritional rehabilitation (Sandboge et al. 2013; Breij, Kerkhof, and Hokken-Koelega 2014). Additionally, the propensity to accumulate fat in the liver might differ between the oedematous (kwashiorkor) and non-oedematous (marasmus) forms of malnutrition as we previously demonstrated that adult survivors of marasmus (MRs) have more liver fat than adult survivors of kwashiorkor (KWs) (Thompson et al. 2022). However, the reason for this finding is not clear.

Outside the nutrition rehabilitation context, greater and faster childhood weight gains have been reported to influence the development of fatty liver. Faienza et al (Faienza et al. 2013). compared 23 children who were small for gestational age (SGA) and experienced rapid weight gain within the first 6-12 months to 24 children whose BWs were appropriate for gestational age (AGA). Fatty liver disease, as measured by abdominal ultrasonography, was observed in 35% of SGA children and was cited as an emerging problem in SGA pre-pubertal children who experienced rapid weight gain in postnatal life (Faienza et al. 2013). Additionally, greater gains in weight-for-age between 1 and 10 years of age were associated with liver fat (by ultrasonography) in adolescents from a South-west England population-based birth cohort (Anderson et al. 2014).

Established inpatient management of SAM begins with an acute “stabilisation” phase in which a diet of 80-100kcal/kg/day is fed to provide energy for weight maintenance, while infections and fluid imbalance are treated (WHO 1999). Once clinical improvement, loss of all oedema, and improved appetite and affect are achieved, the “rehabilitation” phase begins, during which children are fed increasing amounts of energy and protein enriched feeds to allow for attainment of a healthy body weight. WHO recommends that optimal weight gain during this period is >10 g/kg/day (Ashworth et al. 2003). The final phase of treatment, referred to as “recovery”, involves weaning the child to an age-appropriate diet before discharge from hospital.

Jamaican children with marasmus are reported to weigh less at birth (Forrester et al. 2012), and are more wasted and stunted on admission to hospital (Walker and Golden 1988) than children with kwashiorkor. We hypothesized that, in the context of severe acute malnutrition, total and faster weight gain during nutritional rehabilitation and post-hospitalization are associated with greater liver fat in adult survivors. We also hypothesized that adult survivors of marasmus would have more liver fat than adult survivors of kwashiorkor due to their lower BW. This study therefore investigated the relationships between gains in weight and height (during and immediately after SAM rehabilitation) and adult liver fat.

## METHODS

### STUDY DESIGN/ SUBJECTS

A retrospective cohort was assembled after reviewing the medical records of children admitted to the Tropical Metabolism Research Unit (TMRU) Ward with a diagnosis of

severe acute malnutrition between 1963 and 1993. At the time of admission, the Wellcome criteria was used to classify children as having marasmus: weight-for-age < 60% or kwashiorkor: 60-80% weight-for-age, plus oedema, in comparison to the National Centre for Health Statistics (NCHS) standard growth curves (“Classification of Infantile Malnutrition” 1970).

A total of 1,336 children were admitted to hospital with a diagnosis of severe acute malnutrition between 1963 and 1993. We traced 729 of them as adults, and, of that number, 316 underwent basic anthropometry (Forrester et al. 2012) and 92 consented to undergo abdominal CT scans (Figure 1) to estimate liver fat. We decided *a priori* to exclude from the study persons with sickle cell haemoglobinopathy, a history of liver disease or taking medications that cause hepatic abnormalities and to exclude from the analyses participants with a self-reported alcohol intake of more than 14 drinks per week (males) and more than 7 drinks per week (females) (Zeb et al. 2012).

The Mona Campus Research Ethics Committee of the University of the West Indies approved the study protocol (ECP17, 14/15), and each participant gave written informed consent. At the time of admission to hospital (as children), written informed consent was obtained from the parent/guardian of each participant under 18 years of age for medical records to be used for research.

### PAEDIATRIC MEASUREMENTS

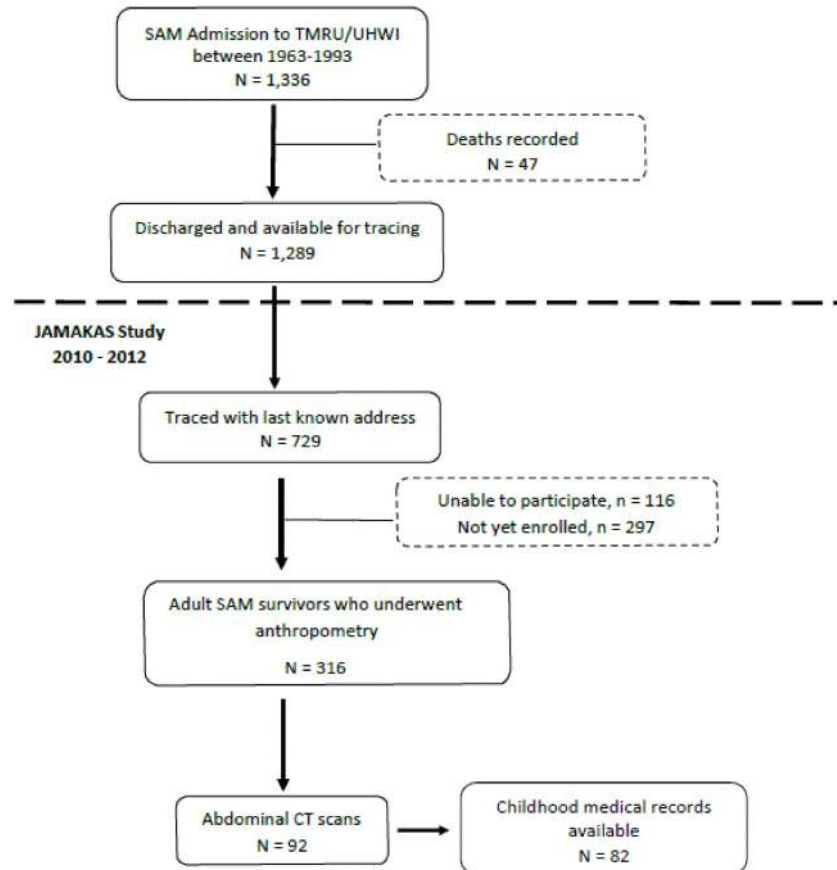
Recorded birth weights and height and weight measurements taken at and during hospitalization were abstracted from hospital records. As children were followed up for a minimum of 2 years after discharge from hospital, height and weight measurements collected over this period were also available for abstraction. The inpatient weight and height measurements were carried out by research nurses trained in anthropometric measurements in infants and children. Length was measured weekly using an infantometer and children were weighed daily using a digital scale. Outpatient measurements were taken either at the TMRU clinic or during a home visit. In the latter case a portable stadiometer (Seca 213) and scale were used.

Rates of weight gain were calculated over 2 time periods as follows:

1. During the rehabilitation phase i.e., the weight difference between weights recorded from the beginning of rehabilitation feeds (when all oedema had resolved) to the end of the rehabilitation phase).
2. In the post-hospitalization period (discharge weight to final follow-up weight).

Rates of height gain were calculated over 2 time periods as follows:

1. During rehabilitation phase i.e., height recorded from the beginning of rehabilitation feeds (when all oedema had resolved) to the end of rehabilitation phase.
2. In the post-hospitalization period (discharge height to final follow up height). Where there was no height



**Figure 1. Flow chart detailing recruitment of adult survivors of SAM in childhood ( $n = 82$ ). SAM, severe acute malnutrition, “unable to participate” includes adult survivors of SAM who had migrated ( $n = 53$ ), were ill ( $n = 19$ ), declined to participate ( $n = 14$ ) or were pregnant ( $n = 30$ ).**

TMRU, Tropical Metabolism Research Unit; UHWI, University Hospital of the West Indies; JAMAKAS, Jamaica Marasmus and Kwashiorkor Adult Survivors.

recorded on discharge, the last height recorded before discharge from hospital was used.

#### ADULT MEASUREMENTS

After a 10-hour overnight fast, participants reported to the TMRU where they completed a staff-administered questionnaire. Body weight was measured to the nearest 0.1 kg and height and waist circumference to the nearest 0.1 cm while wearing light clothing using a standardized protocol (Boyne et al. 2010).

#### LIVER FAT

Abdominal CT scans (Phillips Brilliance 64-slice scanner) were conducted to measure liver fat. A 5 mm CT scan was taken at the T12/L1 intervertebral disc space to include both the liver and the spleen. Using eFilm Workstation 3.1 (Merge Healthcare, Chicago, IL, USA), three regions of interest were placed in the liver and one in the spleen and attenuation readings taken. A mean liver attenuation (MLA) of  $< 40$  Hounsfield Units (HU) and liver spleen: ratio (L/S)  $< 1$  denoted hepatic steatosis  $> 30\%$ .

#### STATISTICAL ANALYSIS

SPSS 19.0 for Windows was used for the statistical analyses. Characteristics of the survivors of marasmus and kwashiorkor were compared using the independent T test. Multivariate regression analyses were conducted with models adjusting for sex, adult age and BMI / fat mass, as all are documented to be associated with fatty liver. Two-sided  $p$ -values were reported and a  $p$ -value  $\leq 0.05$  considered statistically significant.

#### RESULTS

All 92 participants who consented to have abdominal CT scans were included, i.e., no participant was excluded based on the exclusion criteria. However, as childhood hospital records were available for only 82 of these participants, this was the final number of participants whose data were analyzed (Figure 1).

The mean (SD) age of the 82 adult survivors was 28.8 (8.5) years, BMI was 23.8 (5.6) kg/m<sup>2</sup>, MLA was 64.0 (4.7), HU and liver:spleen ratio (L/S) was 1.3 (0.19). 42 (51%) had been diagnosed with marasmus and 40 with kwashiorkor as

**Table 1. Summary of birth weight, admission anthropometry and gains in weight and height during and after hospital admission for SAM.**

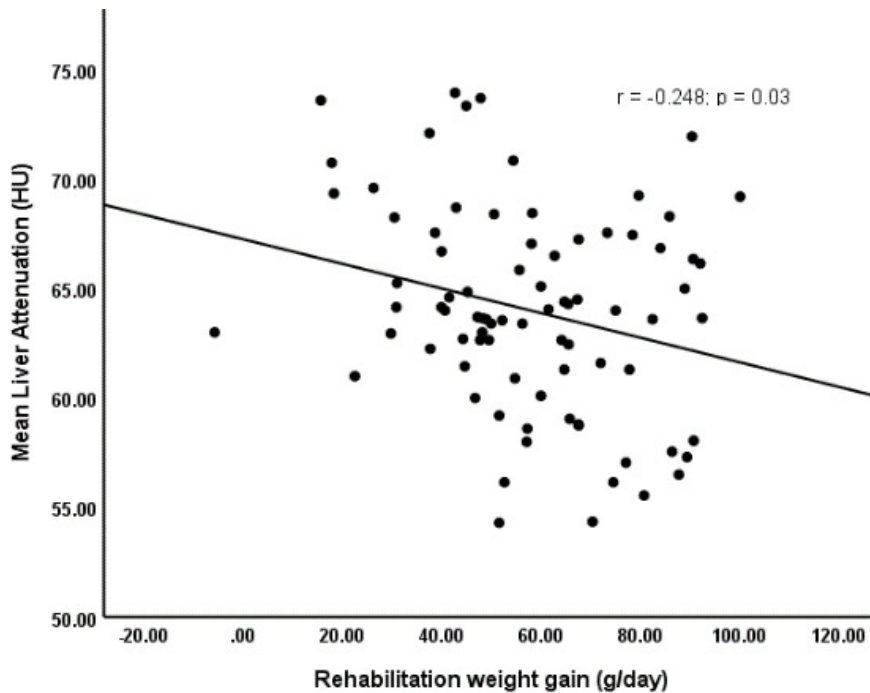
	Marasmus (N=42)	Kwashiorkor (N=40)	P-value (MRs vs. KWs)
Birth Weight (kg)	2.5 ± 0.8	3.0 ± 0.7	0.01
<b>Admission</b>			
Age (days)	364.2 ± 150.0	347.8 ± 128.7	0.60
Sex (% male)	55%	50%	
Weight (kg)	5.1 ± 1.2	6.3 ± 1.3	< 0.001
Height/ Length (cm)	64.6 ± 6.8	66.1 ± 5.9	0.32
Weight-for-age z-score (WAZ)	-4.9 ± 1.2	-3.2 ± 1.1	<0.001
Length/height-for-age z-score (HAZ)	-4.0 ± 1.9	-3.2 ± 1.3	0.031
Weight-for-length z-score (WHZ)	-3.8 ± 0.9	-1.8 ± 1.2	<0.001
<b>Rehabilitation Phase (minimum weight to maximum weight)</b>			
Absolute weight gain (kg)	2.0 ± 0.8	1.7 ± 0.9	0.13
Weight gain (g/d)	53.3 ± 17.6	62.3 ± 23.3	0.053
Weight gain (g/kg/d)	9.2 ± 4.0	9.3 ± 3.2	0.92
Change in weight-for age z-score (ΔWAZ)	2.2 ± 0.9	1.9 ± 0.9	0.13
Absolute height gain (cm)	1.6 ± 1.9	1.0 ± 1.2	0.45
Height gain (cm/y)	12.2 ± 14.0	13.5 ± 11.5	0.83
<b>Post-hospitalization Phase (from discharge up to 2 years follow up)</b>			
Weight gain (g/d)	3.9 (1.0, 7.3)	6.8 (5.2, 9.0)	0.18
Weight gain (g/kg/month)	14.2 ± 18.2	19.9 ± 33.7	0.39
Change in WAZ/month (ΔWAZ)	-0.004 ± 0.14	0.005 ± 0.27	0.43
Height gain from last height during admission (cm/y)	11.7 ± 3.5	15.4 ± 7.4	0.08
Height gain from 1 <sup>st</sup> discharge height (cm/y)	13.0 ± 5.5	14.9 ± 7.7	0.37
Change in HAZ/month (ΔHAZ)	0.11 ± 0.18	0.09 ± 0.12	0.63
<b>Adult Anthropometry, Body Composition and Liver Fat</b>			
Age (years)	26.7 ± 7.6	31.1 ± 8.9	0.02
BMI (kg/m <sup>2</sup> )	22.4 ± 5.5	25.3 ± 5.4	0.02
Lean Mass (kg)	45.7 ± 9.0	48.3 ± 9.7	0.21
Fat Mass (kg)	13.3 ± 13.1	18.5 ± 13.9	0.09
MLA (HU)	63.5 ± 4.4	64.6 ± 5.0	0.29
L/S	1.2 ± 0.2	1.3 ± 0.2	0.65

WAZ- weight for age z-scores, HAZ- height-for-age z scores, MLA-mean liver attenuation, HU-Hounsfields Units, L/S - Liver/spleen attenuation ratio

children. The participants' mean (SD) BW was 2.7 (0.8) kg, and on admission: age, 11.7 (4.6) months, weight, 5.6 (1.4) kg, height, 65.3 (6.4) cm, WHO weight-for-age z-scores, -4.05 (1.41) (Table 1). The mean (SD) rate of weight gain during rehabilitation was 9.3 (3.6) g/kg/day (Table 1).

MRs had a lower BW, and, on admission to hospital, they weighed less and had lower weight-for-age z-scores (WAZ), were more stunted using height-for-age z-scores (HAZ) and were more wasted using weight-for-length z-scores (WLZ) than KWs (Table 1). Rates of rehabilitation weight gain were similar in MRs and KWs using g/d ( $p = 0.053$ ), g/kg/day ( $p = 0.69$ ) and change in WAZ ( $\Delta$ WAZ) ( $p = 0.13$ ) (Table 1). As adults, KWs were older than MRs and had a higher BMI ( $p = 0.02$ ) (Table 1).

Among these adult survivors of severe acute malnutrition, the rate of weight gain during rehabilitation (in g/d) was inversely associated with MLA adjusting for age and sex ( $r = -0.247$ ,  $p = 0.027$ ), and after additionally adjusting for adult BMI ( $r = -0.246$ ,  $p = 0.028$ ) (Figure 2) or fat mass ( $r = -0.247$ ,  $p = 0.028$ ). Rehabilitation weight gain expressed as g/kg/day was inversely associated with MLA adjusting for age and sex ( $r = -0.224$ ;  $p = 0.045$ ) and after additionally adjusting for fat mass ( $p = 0.05$ ) but not after adjusting for BMI ( $p = 0.053$ ). This effect of rehabilitation weight gain (in g/kg/day) on MLA did not depend on the value of adult BMI ( $p = 0.71$ ). However, rehabilitation weight gain expressed as  $\Delta$ WAZ was not related to MLA ( $p = 0.28$ ). Height gain during rehabilitation was not related to MLA or L/S ( $p > 0.6$ ). Post-



**Figure 2. Correlation between mean liver attenuation and rate of rehabilitation weight gain (age, sex and BMI-adjusted) in adult survivors of SAM.**

hospitalization weight and height gain were not associated with MLA or L/S ( $p \geq 0.052$ ) (data not shown).

**Effect of diagnosis:** When the participants were grouped by diagnosis (i.e., MRs and KWs), and regression analyses were adjusted for age, sex and BMI, faster rehabilitation weight gain (g/d) had a negative association with both MLA (difference =  $-0.11 \pm 0.04$ ,  $p = 0.003$ ) (Table 2) and L/S (difference =  $-0.004 \pm 0.002$ ,  $p = 0.024$ ) in MRs. However, among these marasmus survivors, MLA was not associated with rehabilitation weight gain expressed in g/kg/day ( $p = 0.15$ ) or change in WAZ ( $p = 0.25$ ); the same is true for LS ( $p > 0.3$ ). In KWs, rehabilitation weight gain was not associated with MLA in a regression model adjusting for age, sex and adult BMI. However, height gain post-discharge (cm/year) was negatively associated with MLA in KWs (difference =  $-0.384 + 0.12$ ,  $p = 0.006$ ) (Table 2).

**Effect of birth weight:** In these participants, BW was not associated with adult liver fat ( $p = 0.10$ ) adjusting for age, sex and BMI. After additionally adjusting the model for BW, the relationship between rehabilitation weight gain and MLA observed in MRs ( $p = 0.021$ ) (Table 2) remained significant, but the inverse association between rehabilitation weight gain (g/day) and MLA seen in all the participants was no longer significant ( $p = 0.052$ ). The interaction term (BW and rehabilitation weight gain) was not significant ( $p = 0.39$ ). In KWs, although adjusting for BW did not affect the associations between post-hospitalization height gain and MLA, it revealed an association between rehabilitation weight gain and MLA (Table 2).

**Effect of admission HAZ:** Adjusting for age, sex, BMI and admission HAZ, there was an inverse association between rate of rehabilitation weight gain and mean liver attenuation ( $p = 0.03$ ) among all the participants, and this re-

lationship was also significant in MRs ( $p = 0.008$ ). In KWs, the inverse correlation between rate of height gain and mean liver attenuation remained significant when the age, sex and BMI-adjusted regression was further adjusted for HAZ ( $p = 0.003$ ) (Table 2).

**Effect of admission WLZ:** In general, WLZ on admission had no relationship with either outcome measure of liver fat adjusting for age, sex and BMI ( $p$ -values  $> 0.7$ ). In MRs, adding admission WLZ to the age, sex and BMI-adjusted regression model did not affect the inverse association between rate of rehabilitation weight gain and MLA ( $p = 0.002$ ). Similarly, adjusting for admission WLZ on admission in KWs did not alter the inverse relationship between height gain and MLA ( $p = 0.014$ ) (Table 2).

**Effect of admission WAZ:** In our sample, weight for age and weight for height at admission were strongly correlated ( $r = 0.68$ ,  $p < 0.001$ ). Admission WAZ was associated with rehabilitation weight gain (g/day) even after adjusting for age and sex ( $r = 0.25$ ;  $p = 0.025$ ). Despite this, the inverse association between rehabilitation weight gain (g/day) and MLA seen in all the malnutrition survivors remained significant ( $p = 0.03$ ) after adjusting for admission WAZ (data not shown).

## DISCUSSION

This study investigated the associations between weight and height gain during and after hospitalization for SAM in early childhood and adult liver fat in an Afro-Caribbean population. Our findings supported our hypothesis that, in survivors of severe acute malnutrition in childhood, there is a direct association between faster rehabilitation weight gain (g/day) and adult liver fat. This association between

**Table 2. Multivariate age-and-sex-adjusted regression analyses of selected growth variables against mean liver attenuation by diagnosis of SAM (models shown)**

	Mean Liver Attenuation (Hounsfield Units)											
	Age, Sex, BMI			Age, Sex, BMI + Birth Weight			Age, Sex, BMI + Admission WLZ			Age, Sex, BMI + Admission HAZ		
	B	SE	P	B	SE	P	B	SE	P	B	SE	P
<b>All Malnutrition Survivors</b>												
Rehabilitation Weight Gain (g/day)	-0.06	0.02	0.03	-0.06	0.03	0.052	-0.06	0.02	0.02	-0.06	0.03	0.03
Height Gain Post-Discharge (cm/yr)	-0.22	0.11	0.058	-0.23	0.12	0.054	-0.20	0.12	0.09	-0.24	0.11	0.03
<b>Survivors of Marasmus</b>												
Rehabilitation Weight Gain (g/day)	-0.11	0.04	0.003	-0.11	0.04	0.02	-0.12	0.04	0.002	-0.10	0.04	0.008
Height Gain Post-Discharge (cm/yr)	0.12	0.25	0.63	0.21	0.43	0.63	0.095	0.24	0.69	0.13	0.26	0.63
<b>Survivors of Kwashiorkor</b>												
Rehabilitation Weight Gain (g/day)	-0.3	0.04	0.4	-0.1	0.045	0.042	-0.04	0.04	0.26	-0.034	0.04	0.33
Height Gain Post-Discharge (cm/yr)	-0.38	0.12	0.006	-0.40	0.10	0.01	-0.33	0.12	0.014	-0.39	0.11	0.003

Key: WLZ- weight for length z-scores, HAZ- height-for-age z scores, B- unstandardised regression coefficient, SE- standard error, P-p-value

rehabilitation weight gain and adult liver fat was also specifically seen in marasmus survivors. We also demonstrated a direct relationship between post-hospitalization height gain (cm/year) in childhood and adult liver fat in kwashiorkor survivors only.

In a group of Indian children, those in the lowest WHZ tertile were reported to have greater total weight gain, faster weight gain (g/kg/day) and greater increase in WHZ score at 1 month during nutritional rehabilitation when compared to the children in the highest tertile of WHZ (Radhakrishna et al. 2010). Conversely, in our participants, admission WAZ, but not admission WHZ, was positively associated with faster rehabilitation weight gain (g/day). Despite this, neither admission weight, admission WAZ nor minimum weight during admission influenced the association between rehabilitation weight gain and adult liver fat.

WHO recommends a vigorous approach to feeding during the rehabilitation phase, aimed at achieving weight gain of >10 g/kg/d (Ashworth et al. 2003). However, our participants, with a mean rehabilitation weight gain of 9.3 g/kg/day, already appear to be at greater risk of fatty liver as adults. As this association is influenced by adult BMI, the suggestion is that it might be important that these SAM survivors remain within normal BMI limits, along with other lifestyle modifications, to reduce the risk of later liver fat accumulation.

Despite kwashiorkor and marasmus survivors having similar rates of weight gain during the rehabilitation phase of SAM treatment, rate of rehabilitation weight gain was only associated with liver fat in marasmus survivors. Given their lower BW, and in keeping with the thrifty phenotype hypothesis (Hales and Barker 2001), marasmus survivors may be less well adapted to a calorie-surfeit environment than kwashiorkor survivors and might be predisposed to cardiometabolic risk later in life. Thus MRs, who were smaller on admission to hospital than KWs, might be better adapted to a lower rate of weight gain. We further posit that after a nutritional insult in utero, MRs could be predisposed to one pattern of adipogenesis (the process by which mature adipocytes develop), while KWs, with an initial normal growth trajectory in utero, are predisposed to another pattern. Following an adverse *in utero* development, fetuses who experienced intrauterine growth retardation display increased lipogenic (fatty acid and subsequent triglyceride synthesis in both liver and adipose tissue) and adipogenic (differentiation of pre-adipocytes into mature fat cells) capacity in adipocytes (Sarr, Yang, and Regnault 2012). This developmental process of adipogenesis has been shown to occur between 14–23 weeks of gestation, after which the total number of fat lobules remains approximately constant (Poissonnet, Burdi, and Garn 1984). Using mice, Bieswal et al demonstrated that the size distribution of adipocytes as well as adipose tissue growth were both sensitive to the type of nutrient restriction and the time at which early malnutrition occurred (Bieswal et al. 2006). Furthermore, during their intrauterine development, small Indian babies had small abdominal organs and reduced lean mass, but maintained adiposity, and Yajnik et al (Yajnik et al. 2003). posit that this body composition may persist postnatally. If that

is so, the possibility exists that MRs, who were smaller at birth than KWs, might be predisposed to laying down fat as visceral adipose tissue. However, given the age of our participants, it is difficult to say whether this is purely an effect of the timing of the nutritional insult or the effect of accumulated insults.

Low BW, a proxy for poor intrauterine nutrition, has long been associated with adverse long-term outcomes related to non-communicable diseases (NCDs). Indeed, in a systematic review of 57 studies describing the relationships between low BW, rehabilitation growth and features of the metabolic syndrome (Nobili et al. 2008), it was concluded that both low BW and rehabilitation-growth were associated with aspects of subsequent metabolic syndrome. While these findings were not specific to liver fat, non-alcoholic fatty liver disease is widely regarded to be associated with many of the features of metabolic syndrome (Paschos and Paletas 2009; Sundaram, Zeitler, and Nadeau 2009).

Unexpectedly, among our participants, the association between rehabilitation weight gain and adult liver fat was not influenced by BW. While adjusting for BW did not affect the effect of rehabilitation weight gain on adult liver fat, we acknowledge that this could represent over-adjusting as MRs had a lower mean BW than KWs. The fact that BW is not contributory in this cohort of SAM survivors might mean that low BW in this group of participants may not reflect intrauterine undernutrition occurring during those critical windows of developmental plasticity that could lead to abnormal organ development and later NCD risk.

In kwashiorkor survivors, post-hospitalization height gain was associated with adult liver fat and this association was not influenced by adult height. However, gains in height are typically associated with favorable cardiovascular outcomes in adults (Krishnaveni et al. 2015). For example, greater adult height was associated with lower risk of NAFLD among males and females in China in a prospective cohort study of more than 35,000 participants aged 25 years or over with height measured at baseline (Kumari et al. 2020). However, there is recent evidence that suggests that gains in height can also be associated with adverse outcomes, as greater height at birth, or height gain at 0–3 months of age and 6–8 years of age all were associated with higher adult cardiovascular risk traits in 2,218 adults from a birth cohort in India (Antonisamy et al. 2017). While these associations were attenuated when the analyses were adjusted for BMI and adult height (Antonisamy et al. 2017), the same was not true for our participants in whom neither height at admission nor adult height influenced the association between post-hospitalization height gain and liver fat. While there are likely other intervening factors that influence the association, it is possible that, in children who were normal weight at birth, height gain occurring during certain critical windows could represent a similar risk for cardio-metabolic disease as increased adiposity.

## STRENGTHS AND LIMITATIONS

The present study utilized a well-characterized cohort and the use of computed tomography allowed for objective, reproducible, quantitative data. This was supported by the

availability of daily weight and weekly length/height measurements throughout hospitalization. The mortality rate was low, so our findings are unlikely to be confounded by a survival effect. We cannot completely exclude the possibility of selection bias in choosing the 92 participants who underwent abdominal CT scans. Also, since several of the relationships we found not to be significant had  $p$ -values close to 0.05, it is possible that this lack of statistical significance was due to Type 2 errors that would be rectified by a larger sample size. While the lack of data on current diet was also a limitation, we posit that most of these SAM survivors remained in a non-obesogenic environment, as they remained lean on average. We also acknowledge that, along with diet, other intervening factors such as physical activity could influence liver fat in these adult SAM survivors. Additionally, computed tomography is known to be a less sensitive measure of liver fat than magnetic resonance spectroscopy. Finally, the study was also influenced by taking place in a relatively young, lean study population in whom the prevalence of fatty liver is likely to be low.

## CONCLUSIONS

Faster weight gain during treatment for childhood severe acute malnutrition is associated with greater adult liver fat in this Afro-Caribbean population. Rehabilitation weight and post-hospitalization height gain are positively associated with liver fat in marasmus and kwashiorkor survivors respectively. The influence of BW was not established in these participants and may reflect the timing of the nutritional insult in utero. Efforts at rehabilitation must be prudent and guided by the evidence, specifically the recommendations of the WHO (Ashworth et al. 2003). Nevertheless, our data underscores the need to re-examine malnutrition treatment guidelines and optimize rehabilitation weight gain targets in children with severe acute malnutrition.

These data suggest that, along with other lifestyle practices, it might be important for survivors of severe acute malnutrition to maintain a normal BMI throughout their lifespan to prevent cardiometabolic risk and fatty liver disease in later life. The findings and conclusions of the present study are exploratory, and further studies with larger sample sizes are needed to elucidate this important topic.

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## AUTHOR CONTRIBUTIONS

DT, AB, MB, CT-B, IT, and TF designed the research, IT, DS, DT and KM participated in data collection and coordinating the clinical samples. DT and KM analyzed the data. DT conducted the literature review and wrote the first draft of the manuscript and MB had responsibility for final content. All authors read, contributed to, and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to declare.

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