Long-term outcomes after severe childhood malnutrition in adolescents in Malawi (LOSCM): a prospective observational cohort study

Amir Kirolos, Philliness P Harawa, Takondwa Chimowa, Oscar Divala, Bridget Freyne, Angus G Jones, Natasha Lelijveld, Samantha Lissauer, Kenneth Maleta, Melissa J Gladstone, Marko Kerac*, for the CHANGE study collaborators group†*

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*Joint senior authors

†Members listed in the appendix (p 28)

Department of Women and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK (A Kirolos MBChB, Prof M J Gladstone MD); **Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi** (A Kirolos, B Freyne PhD, S Lissauer PhD); **Department of Paediatrics and Child Health** (P P Harawa MBBS, B Freyne), **and Department of Public Health and Family Medicine** (O Divala MSc, Prof K Maleta PhD), **Kamuzu University of Health Sciences, Blantyre, Malawi; Department of Paediatrics, Zomba Central Hospital, Zomba, Malawi** (T Chimowa FCPaed[SA]); **School of Medicine, University College Dublin, Dublin, Ireland** (B Freyne); **Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK** (A G Jones PhD); **Department of Population Health, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK** (N Lelijveld PhD, M Kerac PhD); **Emergency Nutrition Network, Kidlington, UK** (N Lelijveld); **Institute of Infection, Veterinary, and Ecological Sciences, University of Liverpool, Liverpool, UK** (S Lissauer); **Centre for Maternal, Adolescent, and Reproductive Child Health (MARCH), London School of Hygiene and Tropical Medicine, London, UK** (M Kerac)

Summary

Background Research on long-term outcomes of severe childhood malnutrition is scarce. Existing evidence suggests potential associations with cardiometabolic disease and impaired cognition. We aimed to assess outcomes in adolescents who were exposed to severe childhood malnutrition compared with peers not exposed to severe childhood malnutrition.

Methods In Long-term Outcomes after Severe Childhood Malnutrition (LOCSM), we followed up adolescents who had 15 years earlier received treatment for severe childhood malnutrition at Queen Elizabeth Central Hospital in Blantyre, Malawi. Adolescents with previous severe childhood malnutrition included in LOCSM had participated in an earlier follow-up study (ChroSAM) at 7 years after treatment for severe childhood malnutrition, where they were compared to siblings and age-matched children in the community without previous severe childhood malnutrition. We measured anthropometry, body composition, strength, glucose tolerance, cognition, behaviour, and mental health during follow-up visits between Sept 9, 2021, and July 22, 2022, comparing outcomes in adolescents exposed to previous severe childhood malnutrition with unexposed siblings and adolescents from the community assessed previously (for ChroSAM) and newly recruited during current follow-up. We used a linear regression model to adjust for age, sex, disability, HIV, and socioeconomic status. This study is registered with the International Standard Randomised Controlled Trial Number Registry (ISRCTN17238083).

Findings We followed up 168 previously malnourished adolescents (median age 17·1 years [IQR 16·5 to 18·0]), alongside 123 siblings (18·2 years [15·0 to 20·5]), and 89 community adolescents (17·1 years [16·3 to 18·1]). Since last measured 8 years previously, mean height-for-age Z (HAZ) scores had improved in previously malnourished adolescents (difference 0·33 [95% CI 0·20 to 0·46]) and siblings (0·32 [0·09 to 0·55]), but not in community adolescents (difference –0·01 [–0·24 to 0·23]). Previously malnourished adolescents had sustained lower HAZ scores compared with siblings (adjusted difference –0·32 [–0·58 to –0·05]) and community adolescents (–0·21 [–0·52 to 0·10]). The adjusted difference in hand-grip strength between previously malnourished adolescents and community adolescents was –2·0 kg (–4·2 to 0·3). For child behaviour checklist internalising symptom scores, the adjusted difference for previously malnourished adolescents was 2·8 (0·0 to 5·5) compared with siblings and 2·1 (–0·1 to 4·3) compared with community adolescents. No evidence of differences between previously malnourished adolescents and unexposed groups were found in any of the other variables measured.

Interpretation Catch-up growth into adolescence was modest compared with the rapid improvement seen in childhood, but provides optimism for ongoing recovery of height deficits. We found little evidence of heightened non-communicable disease risk in adolescents exposed to severe childhood malnutrition, although long-term health implications need to be monitored. Further investigation of associated home and environmental factors influencing long-term outcomes is needed to tailor preventive and treatment interventions.

Funding The Wellcome Trust.

Introduction

Severe malnutrition in childhood remains prevalent and problematic globally due to issues including food insecurity, conflict, and climate change.[1] Severe wasting and oedematous malnutrition, often labelled together as severe acute malnutrition (SAM), are particularly serious forms of malnutrition. Severe wasting alone is responsible for over 500 000 deaths per year worldwide; the number of children with oedematous malnutrition is uncertain and underestimated.[2,3] Prompt treatment can partly avert the very high risk of death in the short term, although mortality is high even after discharge from care.[4] Research on severe childhood malnutrition has therefore mainly focused on the acute presentation when mortality is highest, but more research on long-term outcomes is needed given that an increasing number of

Research in context

Evidence before the study

Survival from severe childhood malnutrition has improved in recent years, but most research remains focused on the acute presentation and the first 1000 days of life (ie, from conception to age 2 years). Few studies have investigated long-term outcomes in survivors, but research suggests potential long-term adverse effects, including impaired growth, altered body composition, greater cardiometabolic disease risk, cognitive impairment, and behavioural problems. A 2021 systematic review looked at the risk of cardiometabolic non-communicable disease (NCD) in later life with a search strategy focusing on "severe childhood malnutrition", "famine", and "cardiometabolic NCDs" to identify studies in MEDLINE, Embase, Global Health, and the Cumulative Index to Nursing and Allied Health Literature. This review of studies, published between 1968 and 2019, found that severe malnutrition in childhood was associated with increased risk of cardiovascular disease, hypertension, impaired glucose metabolism, and metabolic syndrome in later life. A separate 2022 systematic review looked at cognition, behaviour, and mental health in those exposed to severe childhood malnutrition with a search strategy focusing on "severe acute malnutrition", "cognition", "behaviour", and "mental health" to identify studies in MEDLINE, Embase, Global Health, and PsycINFO. This review of studies, published between 1995 and 2021, found weak evidence (due to a lack of studies) of a link with specific mental health disorders, and moderate evidence of a link with impaired cognition and behavioural problems. We reviewed studies published up to Dec 31, 2022, using the same search strategies and found no additional studies that changed the conclusions of these systematic reviews. Evidence from these reviews is limited by studies with retrospective study designs and confounding factors that are unaccounted for.

Added value of this study

This prospective cohort study is one of few reporting outcomes in adolescence and compares the malnutrition-exposed cohort to unexposed groups at both household and community levels. The improvement in average height-for-age Z score in previously malnourished adolescents was modest compared with the rapid post-discharge catch-up growth previously noted in this cohort, but shows that ongoing recovery of height deficits beyond early childhood into adolescence is possible. We found evidence of hand-grip strength deficits in those exposed to severe childhood malnutrition compared with community adolescents, although grip strength was similar in comparison with siblings. These results contrast with previously recorded weaker grip strengths in childhood compared with both unexposed groups, implying some recovery of strength deficits in comparison with siblings.

Implications of all the available evidence

Survivors of childhood malnutrition can continue to grow and develop well beyond the first 1000 days of life, and support into adolescence should not be neglected. Observed catch-up growth in this malnutrition-exposed cohort might be linked to household and environmental factors common to their siblings. These factors require further investigation as they can be the target of future interventions. Despite an apparent improvement since childhood, our results do not rule out longer-term associations between severe childhood malnutrition and impaired cognition, behavioural, and mental health problems, and a higher risk of cardiometabolic disease. Although we did not find strong evidence of these impairments in our cohort, follow-up into later adulthood is needed, as is research across other settings to establish key factors influencing clinical trajectories after treatment.

Correspondence to:
Dr Amir Kirolos, Department of Women and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L7 8TX, UK
a.kirolos@liverpool.ac.uk

See **Online** for appendix

children with previous severe malnutrition now survive to adulthood.[5]

Impaired growth during episodes of severe malnutrition, rapid feeding during treatment, altered body composition, and poor post-recovery food environments have been implicated in increasing long-term cardiometabolic disease risk.[6–8] In a 2021 systematic review, 15 (63%) of 24 studies linked severe childhood malnutrition with impaired glucose tolerance.[9] This review also found that severe malnutrition in childhood was associated with increased risk of cardiovascular disease (seven [88%] of eight studies), hypertension (eight [73%] of 11 studies), and metabolic syndrome (six [100%] of six studies) in later life. The 2014 Chronic Disease Outcomes following SAM (ChroSAM) study tracked 320 children with previous severe childhood malnutrition 7 years after discharge from inpatient treatment in Blantyre, Malawi, and compared their health outcomes with siblings and children from the community without previous severe malnutrition.[10] The ChroSAM study found high mortality rates in the 7 years following discharge from care, particularly in those with HIV and underlying disabilities. Survivors showed quick catch-up growth in height during childhood but showed evidence of weaker hand-grip strength, lower exercise tolerance, lower lean mass, and stunting compared with siblings and community children without previous severe malnutrition.[10]

Previous research has linked severe childhood malnutrition with impaired function, development, and cognition in middle childhood.[10,11] Furthermore, severe childhood malnutrition has been linked with chronic malnutrition (ie, stunting), which is widely associated in the literature with impaired cognition in the long term.[12] However, an acute episode of severe malnutrition in childhood might independently affect long-term cognitive capacity. A systematic review found strong evidence of an effect on neurodevelopment and moderate evidence of an effect on cognition and behaviour.[12] These findings were limited by many studies not accounting for important confounding variables and by a scarcity of

studies investigating mental health. The ChroSAM study found that children with previous severe malnutrition had lower school achievement compared with those without, but that lower Cambridge Neuropsychological Test Automated Battery (CANTAB) cognition test scores barely differed between groups after adjusting for confounders such as HIV, disability, and socioeconomic status.[13]

Data on long-term outcomes of severe childhood malnutrition are scarce, with many previous studies affected by retrospective study designs and a failure to account for potential confounding factors.[9,11,12] Understanding long-term outcomes of severe malnutrition can provide valuable information on disease risk throughout the life course and inform malnutrition prevention and treatment strategies. In particular, there has been debate on how much catch-up is possible after the first 1000 days of life[14,15]—a particularly sensitive window of growth and development and thus the focus for much current policy, programme, and resource investment.[16,17] With an aim of informing future policy and practice, our objectives were to further follow up an established cohort of adolescents with previous severe childhood malnutrition from Blantyre, Malawi,[10] and assess growth, clinical, and neurodevelopmental outcomes 15 years after discharge. For context, we also compared these outcomes with siblings and adolescents from the same communities without previous severe malnutrition.

For the **protocol** see https://doi.org/10.1186/ISRCTN17238083

Methods

Study design and participants

This prospective cohort study began as a randomised controlled trial (the PRONUT study) testing the use of probiotics and prebiotics in severely malnourished children, in which the intervention showed no overall effect.[18] The PRONUT study recruited 1024 children undergoing inpatient treatment between July 12, 2006, and March 7, 2007, from the nutrition ward in Queen Elizabeth Central Hospital, Blantyre, Malawi (median age at admission 24 months [IQR 16–34]). 477 (47%) of the original cohort were followed up 1 year after discharge as part of the Follow-up after Severe Acute Malnutrition (FuSAM) study focusing on post-discharge growth and mortality.[19] 320 (31%) of the original cohort were then successfully followed up again 7 years after discharge (median age 9·3 years [IQR 8·1–10·3]), along with the recruitment of 219 siblings and 184 children from the community who had not had severe childhood malnutrition (the unexposed group), as part of the ChroSAM study.[10]

The current follow-up (Long-term Outcomes after Severe Childhood Malnutrition [LOSCM] study) was prospectively registered in the International Standard Randomised Controlled Trial Number Registry (ISRCTN17238083). Reporting follows STROBE guidelines. For LOSCM we followed up the ChroSAM study cohort 8 years later, now in adolescence or young adulthood, including the previously malnourished adolescents (the exposed group), and the previously recruited siblings and children from the community (referred to as siblings and community adolescents [the unexposed groups] throughout).[10] Follow-up visits were between Sept 9, 2021, and July 22, 2022. Our study team consisted of nurses from the ChroSAM study, already familiar with the cohort, who contacted participants by telephone and in the community from previous records. We invited participants to attend Queen Elizabeth Central Hospital for half-day assessments. When siblings and community children from the ChroSAM study were not available or declined, we recruited new siblings and adolescents from the community whenever possible to improve study power, using the same methodology as before (ie, available sibling closest in age or nearest neighbour of the same sex who was no more than 1 year older or 1 year younger).[10]

Ethical approval was granted from the Malawi College of Medicine Research Ethics Committee (P.02/21/3269), University of Liverpool Research Ethics committee (reference number 10126), and London School of Hygiene & Tropical Medicine Research Ethics Committee (reference number 26299). We obtained written informed consent from all participants aged 18 years and older, and written assent from participants younger than 18 years with parental or guardian written informed consent.

The protocol is available online on the study's ISRCTN page.

Procedures

Extended data collection methods for exposures and outcomes are provided in the appendix (pp 2–4). Demographic details were collected during the latest follow-up and included HIV status, socioeconomic status (recorded with Malawi 2015 Demographic and Health Survey [DHS] questions asked by study nurses), sex (self-reported by participants; options male or female), pubertal status (self-reported using Tanner staging images and descriptions), and disability (self-reported using Washington Group disability questions). We used the results of the 2015 Malawi DHS principal component analysis to assign a wealth score to each participant on the basis of their responses to DHS questions.[20] We considered participants to be prepubertal when self-reporting a Tanner staging score of 2 or less for both genitalia and pubic hair. We considered participants to have a disability when reporting a score of 3 (ie, a lot of difficulty) or 4 (ie, unable to do) in any domain of the Washington Group disability questions.

We measured selected outcomes using the same methods as the ChroSAM study,[10,13] including anthropometry (ie, height and weight), body composition (ie, bioelectrical impedance analysis [BIA]), waist and hip circumference, hand-grip strength, school achievement, cognition (CANTAB cognition tests [Cambridge Cognition, Cambridge, UK]), blood pressure, fasting glucose, and oral glucose tolerance. Study nurses received

updated training on measurement of all outcomes. Anthropometry followed WHO guidelines[21] with each measurement taken independently by two nurses, checked for concordance, and repeated if measures varied more than prespecified limits.[22] Weight was measured with digital scales (SECA 877, SECA, Hamburg, Germany) and standing height with a height board (SECA 213, SECA, Hamburg, Germany). We used tape measures to measure waist and hip circumference and calculated a waist-to-hip ratio. BIA was measured with a Quadscan 4000 device (Bodystat, Douglas, Isle of Man, UK). Handgrip strength was measured using a Takei Grip-D device (Takei, Niigata, Japan) with the best of three attempts recorded. To assess school achievement, participants reported the highest school year they had attended because students in Malawi only progress to the next school year by passing the previous year rather than by age. Participants completed selected tests as part of the CANTAB cognition assessment with the same methods as used in the ChroSAM study.[13] CANTAB test results for motor screening test mean latency (ms), paired associates learning (PAL) total errors, PAL total errors (six shapes, adjusted), pattern recognition memory (proportion of patterns recognised correctly), intra–extra dimensional set shift (IED) total stages completed, and IED total errors (adjusted) were calculated directly from the CANTAB software (Cambridge Cognition, Cambridge, UK). Blood pressure was measured at rest with a blood pressure monitor (OMRON M6 comfort model, OMRON, Kyoto, Japan). Before attending, participants were asked to fast overnight for 10 h, which was then confirmed by self-report on the morning of assessment. We then sampled venous blood to test fasting glucose and insulin. We conducted oral glucose tolerance tests (OGTT) on a subset of participants who consented to the multiple blood draws required, confirmed that they had followed instructions to fast, and arrived on time to allow sufficient time for the full test. Participants drank 300 mL Rapilose OGTT Solution (Penlan Healthcare, Weybridge, UK) containing 75 mg glucose and had venous blood sampled at 30-min, 60-min, 90-min, and 120-min timepoints after ingestion, which were also tested for glucose and insulin.

We assessed additional outcomes to previous follow-ups, including standing long-jump distance, hair cortisol concentrations, and scores from behaviour and mental health questionnaires. We asked all participants to do a standing long jump from a set mark and measured the distance to their heel using a tape measure, recording the best of three attempts. For participants who had at least 2 cm of hair, we sampled and tested hair cortisol concentrations using previously established methods.[23] Participants completed the Patient Health Questionnaire (PHQ-9) to assess for symptoms of depression and the Generalised Anxiety Disorder assessment (GAD-7) screening questions to assess for symptoms of anxiety. Participants also completed a Strengths and Difficulties Questionnaire (SDQ) to assess behaviour, and primary guardians who attended with participants younger than 18 years completed a Child Behaviour Checklist (CBCL) to assess aspects of both behaviour and mental health. We calculated total SDQ, PHQ-9, and GAD-7 questionnaire scores, and calculated internalising (ie, anxious-depressed, withdrawn-depressed, and somatic complaints) and externalising (ie, rule-breaking and aggressive behaviour) CBCL scores using the Achenbach System of Empirically Based Assessment software (Thomas M Achenbach, Research Center for Children, Youth, & Families, Burlington, VT, USA).

For more on **the Achenbach System of Empirically Based Assessment** see https://aseba.org/software/

Statistical analysis

The sample size of this study was determined by numbers originally recruited to the cohort and lost to follow-up since discharge. On the basis of the primary outcome of growth, we calculated that the study had a post-hoc power of at least 90% to detect a difference of 0·5 height-for-age Z (HAZ) scores or greater (assuming 5% significance level and equal standard deviations in both groups) between previously malnourished adolescents and siblings, and between previously malnourished adolescents and community adolescents.

All analyses were carried out in R software (version 4.0.3). BMI-for-age Z (BAZ) scores and HAZ scores were calculated on the basis of the 2007 WHO growth reference values with the anthroplus package in R. We used the age-19-years reference value for older participants when calculating BAZ and HAZ scores. We calculated the difference in HAZ scores with 95% CIs between the ChroSAM study (7 years after discharge) and current follow-up (15 years after discharge) for exposed and unexposed groups in participants common to both follow-up studies. We analysed BIA data by reporting the measured phase angle at 50 kHz (ie, composite measure of cellular health based on membrane function and lean mass), calculating a lean mass index (1/impedance; ie, measure of lean mass independent of height), and an impedance index (height in m^2/impedance × 10 000; ie, direct estimate of relative lean mass).[24] We calculated homoeostatic model assessment for insulin resistance (HOMA-IR; ie, fasting insulin resistance), Matsuda index (ie, measure of whole-body insulin sensitivity), insulinogenic index (ie, β-cell insulin secretion), and disposition index (ie, ratio of incremental increase in insulin to blood glucose) on the basis of glucose and insulin results from the OGTT.[25,26] 21% of insulin samples were haemolysed when analysed; therefore, when an insulin result for a single timepoint was missing, we imputed the missing value as the midpoint between the adjacent timepoints. Imputed values were used for area-under-the-curve calculations in indices that required all timepoints. Given minor variation on a single imputed timepoint has minimal influence, and exclusion of OGTTs with missing timepoints did not meaningfully change results, we used this method to avoid a large reduction in power.

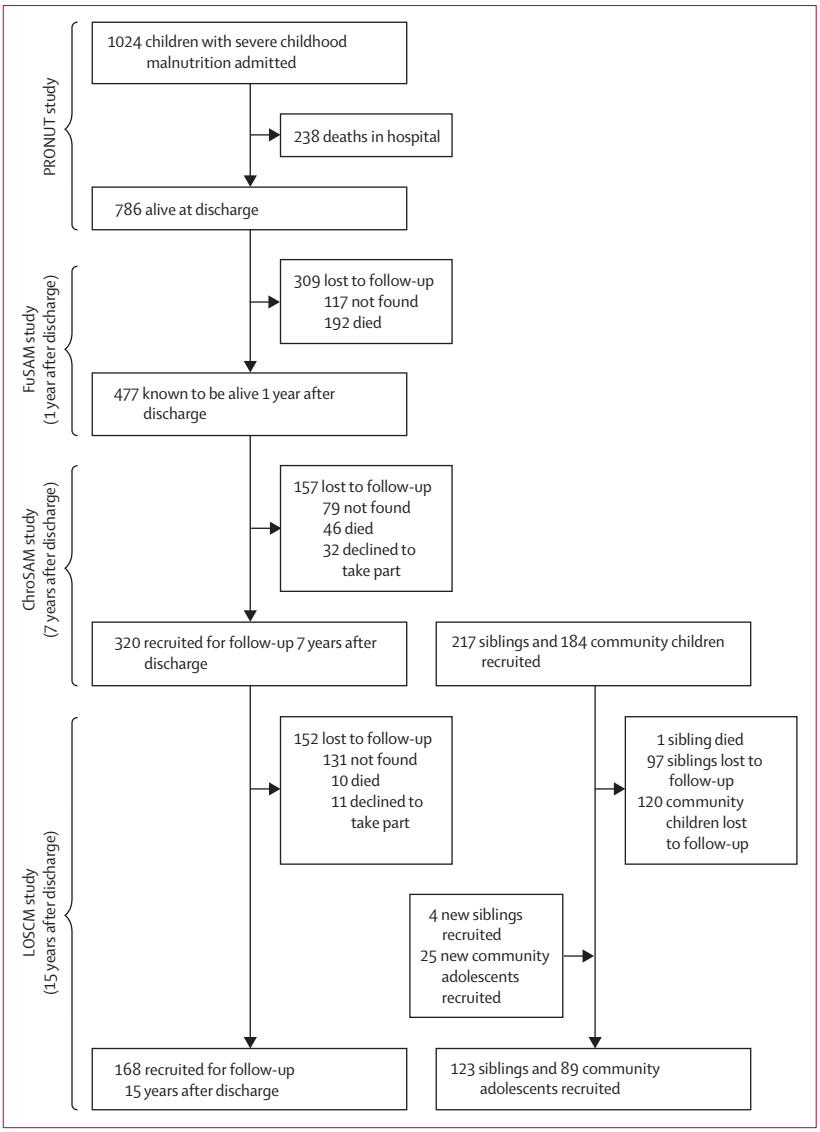

Figure 1: **Recruitment and follow-up of participants**

We did not calculate indices when the baseline fasting insulin value was missing.

We calculated the mean and standard deviation for each outcome in previously malnourished adolescents, siblings, and community adolescents. We compared previously malnourished adolescents to siblings and previously malnourished adolescents to community adolescents separately in our statistical models. We used adjusted linear regression models with outcomes of interest as the response variable, exposure to severe childhood malnutrition as an explanatory variable, and age, sex, HIV status, disability, and socioeconomic status as covariates. Puberty was included as an additional covariate in body composition outcomes. We selected these variables on the basis of previous knowledge of the variables most likely to be confounding factors in this cohort and context. We reported estimated mean differences in outcomes, with corresponding 95% CI and p values, associated with exposure to severe childhood malnutrition from the adjusted linear regression models. Multivariable-ordered logistic regression was used for school achievement and IED (total stages) outcomes. We adjusted for the same covariates in these models—age, sex, HIV status, disability, and socioeconomic status—and used model coefficients to determine adjusted mean differences, 95% CIs, and p values. Our study design compared an exposed group to two separate unexposed groups at the household level (eg, siblings who were more likely to share common factors, such as household environment) and at the community level (eg, community adolescents). This study design allows comparison of outcomes across both unexposed groups. We adjusted the linear regression for both groups for known confounders, but not the unmeasured common factors between previously malnourished adolescents and siblings. Therefore, we conducted a sensitivity analysis for the comparison between previously malnourished adolescents and siblings using a mixed linear regression model that included covariates from the general linear regression (ie, age, sex, socioeconomic status, HIV, disability, and pubertal status for body composition outcomes) as fixed factors, in addition to sibling pairs as a random factor, which accounted for the unmeasured commonality between siblings.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

The sampling frame for this study was based on 320 previously malnourished adolescents, 217 siblings, and 184 community adolescents recruited during the ChroSAM study 8 years previously (figure 1). In the current follow-up, we re-recruited 168 (53%) previously malnourished adolescents, 119 (55%) siblings, and 64 (35%) community adolescents. To address the lower numbers of those in unexposed groups, we recruited four new siblings and 25 new community adolescents. 21 (7%) of the 320 families with a previously malnourished adolescent were successfully contacted but not included in the study. Of those, 11 (3%) declined and ten (3%) had died within the 8 years (three of whom had HIV). The remaining 131 (41%) were lost to follow-up due to factors including families being uncontactable over the phone, families or participants having moved house to an unknown new residence, and families or participants having moved to areas distant from Blantyre. Previously malnourished adolescents lost to follow-up had similar demographic characteristics to those retained (appendix p 23).

	Previously malnourished adolescents (n=168)	Siblings (n=123)	Community adolescents (n=89)
Age, years (IQR; range)	17·1 (16·5 to 18·0; 14·9 to 29·1)	18·2 (15·0 to 20·5; 10·4 to 31·3)	17·1 (16·3 to 18·1; 13·5 to 28·8)
Sex			
Male	92 (55%)	44 (36%)	57 (64%)
Female	76 (45%)	79 (64%)	32 (36%)
Birth order	3 (2 to 4)	2 (2 to 3)	2 (1 to 3)
Prepubertal*	5/167 (3%)	10/120 (8%)	0/86
Living with HIV*	59/165 (36%)	9/94 (10%)	2/55 (4%)
Disability	16 (10%)	5 (4%)	2 (2%)
Admitted for hospital treatment in the past year	3 (2%)	2 (2%)	2 (2%)
Previously treated for tuberculosis	11 (7%)	2 (2%)	0
Resides in urban area	90 (55%)	..	39 (44%)
DHS Wealth Score	0·7 (–0·2 to 1·9)	..	0·5 (–0·2 to 1·6)
Reports not eating food during a day in the past week due to food scarcity	49 (29%)	..	26 (29%)
Reports someone smoking in their household	28 (17%)	..	13 (15%)
Mother died*	36/167 (22%)	..	4/89 (4%)
Father died*	43/164 (26%)	..	15/88 (17%)
Mother's age, years	43 (38 to 47)	..	39 (37 to 42)
Unimproved toilets	92 (55%)	..	53 (60%)
Cooking inside with smoke	31 (18%)	..	13 (15%)
Maternal education			
None	23 (14%)	..	10 (11%)
Primary	95 (57%)	..	50 (56%)
Secondary or higher	40 (24%)	..	25 (28%)
Unknown	10 (6%)	..	4 (4%)

Data are median (IQR), n (%), or n/N (%). Prepubertal status was indicated by score of ≤2 in both genital and pubic hair Tanner staging. Disability status was indicated by score of 3 or 4 in any Washington Group disability question. Urban status was defined by housing within Blantyre city directorate. A higher DHS Wealth Score indicates higher socioeconomic status. Unimproved toilets are defined as an open-pit latrine, or use of a field or bush. Cooking inside with smoke was indicated by use of wood or charcoal inside the home. DHS=Demographic and Health Survey. *The lower denominators are because of information being unknown for some participants.

Table 1: **Participant demographic and health characteristics**

As confirmed by self-report, all participants were Malawian from Blantyre and surrounding areas. 92 (55%) of 168 previously malnourished adolescents were male compared with 44 (36%) of 123 siblings and 57 (64%) of 89 community adolescents (table 1). Previously malnourished adolescents had a higher prevalence of HIV (59 [36%] of 165 for whom HIV status was known) compared with siblings (nine [10%] of 94 for whom HIV status was known) and community adolescents (two [4%] of 55 for whom HIV status was known). Previously malnourished adolescents also had a higher prevalence of disability (16 [10%]) compared with siblings (five [4%]) and community adolescents (two [2%]).

Previously malnourished adolescents had lower HAZ scores compared with siblings (adjusted difference –0·32 [95% CI –0·58 to –0·05]), and to a lesser extent compared with community adolescents (adjusted difference –0·21 [–0·52 to 0·10]; table 2; appendix p 24). Compared with data collected 8 years previously, mean HAZ scores improved for both previously malnourished adolescents (difference 0·33 [0·20 to 0·46]) and siblings (difference 0·32 [0·09 to 0·55]), although the HAZ scores of community adolescents remained similar (difference –0·01 [–0·24 to 0·23]; figure 2; appendix p 25).

There was some evidence of lower BAZ scores in previously malnourished adolescents compared with siblings, and there was little evidence of differences in waist-to-hip ratio or lean mass (as measured by impedance and lean mass indices) between exposed and unexposed groups (table 2).

Non-communicable, metabolic disease risk and adjusted differences between exposed and unexposed groups are shown (table 3). Although the point estimate indicated a poorer hand-grip strength in previously malnourished adolescents compared with community adolescents, the 95% CI crossed the null value, and no difference was seen when compared with siblings. There was no evidence of differences between exposed and unexposed groups when comparing blood pressure or hair cortisol, although the analysis of hair cortisol was limited by the low number of participants who had hair long enough to sample. There was also no evidence of differences between exposed and unexposed groups when comparing fasting glucose and

	Previously malnourished adolescents (n=168)	Siblings (n=123)	Previously malnourished adolescents *vs* siblings		Community adolescents (n=89)	Previously malnourished adolescents *vs* community adolescents	
			Adjusted difference	p value		Adjusted difference	p value
HAZ	−1·56 (1·05)	−1·05 (1·01)	−0·32 (−0·58 to −0·05)	0·020	−1·33 (0·85)	−0·21 (−0·52 to 0·10)	0·18
BAZ	−0·54 (0·91)	−0·16 (0·99)	−0·24 (−0·48 to 0·01)	0·056	−0·46 (1·01)	−0·18 (−0·47 to 0·11)	0·23
Phase angle, degrees	6·0° (0·8)	5·9° (0·9)	−0·1 (−0·3 to 0·1)	0·49	6·3° (0·9)	−0·29 (−0·54 to −0·03)	0·025
Impedance index (height [m²]/ impedance)	42·1 (8·9)	41·0 (9·9)	0·4 (−1·6 to 2·4)	0·68	44·6 (9·0)	−1·7 (−4·0 to 0·7)	0·16
Lean mass index (1/impedance × 10 000)	16·7 (2·4)	16·4 (2·5)	0·0 (−0·6 to 0·6)	0·89	17·2 (2·5)	−0·5 (−1·2 to 0·2)	0·15
Waist-to-hip ratio	0·81 (0·05)	0·81 (0·06)	−0·01 (−0·02 to 0·01)	0·47	0·81 (0·05)	0 (−0·02 to 0·02)	0·99

Data are mean (SD) or mean (95% CI), unless otherwise specified. Adjusted differences are derived from linear regression models adjusted for age, sex, disability, socioeconomic status, and HIV status. Linear regression for phase angle, impedance index, lean mass index, and waist-to-hip ratio also includes puberty as a covariate. HAZ=height-for-age Z score. BAZ=BMI-for-age Z score.

Table 2: **Anthropometry, body composition, and adjusted differences between severe childhood malnutrition exposed and unexposed groups**

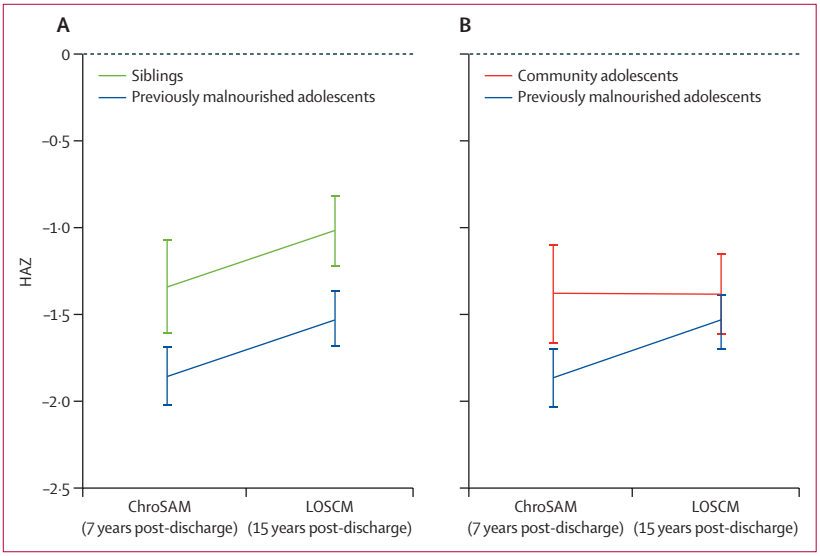

Figure 2: **HAZ scores of participants during the ChroSAM study (7 years after discharge) and at follow-up in the LOSCM study (15 years after discharge)**
Only includes participants common to both timepoints and excludes those lost to follow-up, newly recruited siblings, and newly recruited community adolescents (ie, 168 previously malnourished adolescents, 119 siblings, and 64 community adolescents). Error bars indicate 95% CIs. ChroSAM=Chronic Disease Outcomes following Severe Acute Malnutrition. HAZ=height-for-age Z. LOSCM=Long-term Outcomes after Severe Childhood Malnutrition.

HOMA-IR, or in the subset of participants who underwent an OGTT (n=235) when comparing Matsuda, insulinogenic, and disposition indices.

Participants' school grades achieved, CANTAB cognition tests, behaviour and mental health questionnaire scores, and adjusted differences between exposed and unexposed groups are provided in the appendix (pp 26–27). There was no evidence of differences between exposed and unexposed groups in all CANTAB cognition tests or when comparing school achievement. There was also no evidence of differences in the scores of PHQ-9, GAD-7, and SDQ questionnaires between the exposed and unexposed groups. For CBCL internalising behaviour scores (ie, anxious-depressed, withdrawn-depressed, and somatic complaints), the adjusted difference for previously malnourished adolescents was 2·8 (95% CI 0·0 to 5·5) compared with siblings and 2·1 (−0·1 to 4·3) compared with community adolescents.

Results from unadjusted models are detailed in the appendix (pp 5–10). Analyses stratified by sex and analyses excluding participants living with HIV are shown in the appendix (pp 11–20). In the sensitivity analysis, there was little difference in estimates between models and results from both the mixed effects and linear regression models (appendix pp 21–22).

Discussion

Our study, which followed up a cohort of children 15 years after treatment for severe malnutrition, found evidence of ongoing recovery of height deficits into adolescence. Notably, the HAZ scores of siblings, but not community adolescents, also improved over this period. This finding could indicate that household and environmental factors common to siblings contributed to catch-up growth. This finding requires further investigation because these factors could be the focus of future post-malnutrition interventions, such as improved home-based care, better access to malnutrition treatment programmes and health services, better nutrition and food environment, improved socioeconomic conditions, and improved home environments. Other studies have also observed similar better-than-expected growth after malnutrition, possibly because of a greater focus on children perceived to be vulnerable and treated and supported as such.[27] However, improvement in HAZ scores over later childhood and adolescence was modest compared with rapid growth after discharge,[10] and previously malnourished adolescents had persistently lower HAZ scores than those unexposed. We found that previously malnourished adolescents had weaker handgrip strength than community adolescents, but not when compared with siblings, despite grip-strength deficits compared with both groups when followed-up earlier in childhood during ChroSAM.[10] Although these results

	Previously malnourished adolescents	Siblings	Previously malnourished adolescents *vs* siblings		Community adolescents	Previously malnourished adolescents *vs* community adolescents	
			Adjusted difference	p value		Adjusted difference	p value
Hand-grip strength, kg	30·0 (8·0; n=168)	29·7 (9·4; n=123)	0·1 (–2·0 to 2·2)	0·91	33·0 (7·0; n=89)	–2·0 (–4·2 to 0·3)	0·088
Standing long jump, cm	157·8 (33·8; n=168)	153·9 (31·9; n=123)	–2·7 (–10·8 to 5·4)	0·52	165·9 (31·9; n=89)	–5·5 (–14·9 to 3·9)	0·25
Systolic blood pressure, mm Hg	113·3 (14·9; n=163)	113·6 (13·4; n=123)	0·5 (–3·3 to 4·4)	0·78	116·0 (12·8; n=89)	0·0 (–4·5 to 4·5)	0·98
Diastolic blood pressure, mm Hg	72·4 (10·9; n=163)	72·3 (9·3; n=123)	1·6 (–1·2 to 4·5)	0·26	71·7 (8·4; n=89)	2·6 (–0·7 to 6·0)	0·13
Hair cortisol, pg/mg	10·5 (12·4; n=56)	7·8 (4·5; n=34)	2·4 (–3·4 to 8·1)	0·42	7·9 (9·2; n=21)	2·8 (–5·1 to 10·8)	0·48
Fasting glucose, mmol/L	4·6 (0·4; n=145)	4·7 (0·4; n=107)	0·0 (–0·1 to 0·1)	0·69	4·8 (0·5; n=82)	–0·1 (–0·2 to 0·0)	0·16
120-min glucose, mmol/L	6·0 (0·9; n=103)	6·0 (1·0; n=75)	0·0 (–0·4 to 0·3)	0·97	6·2 (1·2; n=57)	–0·3 (–0·7 to 0·1)	0·14
Matsuda index	5·9 (3·4; n=72)	7·1 (5·6; n=62)	–1·3 (–3·1 to 0·5)	0·16	5·9 (3·4; n=44)	1·1 (–0·4 to 2·5)	0·14
HOMA-IR	1·6 (0·8; n=78)	1·7 (1·1; n=64)	–0·2 (–0·5 to 0·2)	0·37	1·6 (0·9; n=50)	–0·3 (–0·6 to 0·1)	0·15
Insulinogenic index	1·5 (1·0; n=65)	1·4 (1·0; n=54)	–0·1 (–0·5 to 0·3)	0·78	1·2 (0·7; n=40)	0·0 (–0·4 to 0·4)	0·88
Disposition index	7·5 (5·1; n=64)	7·6 (5·6; n=52)	–1·0 (–3·2 to 1·2)	0·36	6·5 (4·9; n=38)	0·5 (–1·8 to 2·7)	0·68

Data are mean (SD) or mean (95% CI), unless otherwise specified. Many participants had hair too short to sample (particularly male participants), resulting in a low sample size for hair cortisol results. Adjusted differences are derived from linear regression models adjusted for age, sex, disability, socioeconomic status, and HIV status. HOMA-IR=homoeostatic model assessment for insulin resistance.

Table 3: **Non-communicable, metabolic disease risk, and adjusted differences between severe childhood malnutrition exposed and unexposed groups**

indicate ongoing strength deficits, they suggest some possible recovery in comparison with siblings. With respect to body composition, blood pressure, glucose tolerance, and cognition, we found little evidence of differences between exposed and unexposed groups.

One of the limitations of our study is the healthy survivor bias. Many children initially recruited as inpatients died in subsequent years following discharge from care, particularly those who had HIV.[10] Ten (6%) of the 168 re-recruited previously malnourished children died in the 8 years before this follow-up: this proportion is high, albeit lower than in earlier years when there was very high post-discharge mortality rates in previous follow-up rounds.[10,19] Participants who died are likely to have been the most susceptible and might have had worse long-term health outcomes had they survived to adolescence. Hence, only the healthiest participants remained in the cohort, meaning potential differences between exposed and unexposed groups might be lessened. Participants lost to follow-up might have also introduced selection bias, although demographic details of those retained in our study were similar to previous follow-ups (appendix p 23). Most participants were post-pubertal, but given that malnutrition can be associated with delayed puberty, HAZ scores based on chronological age and comparisons between exposed and unexposed groups might not accurately reflect growth trajectories. Despite our post-hoc power calculation indicating an adequate sample size for this outcome, lower HAZ scores observed in previously malnourished adolescents compared with unexposed groups should be interpreted in the context of this limitation and the long-term effect might be better estimated after a later follow-up to obtain final adult heights. Another limitation is the absence of detailed information on classic non-communicable disease risk factors. Although exposure to household smoking was similar in the different groups, we did not directly measure diet and exercise. At this age, especially for siblings in the same household, diet and exercise are likely to be similar and thus very unlikely to alter our overall results and conclusions. However, these factors are important to measure in future follow-ups as the cohort ages and lifestyle differences emerge. We found evidence of possible differences in parent-reported CBCL internalising scores (ie, anxious-depressed, withdrawn-depressed, and somatic complaints) but little evidence of differences with other self-reported mental health questionnaires (ie, PHQ-9 and GAD-7). Therefore, this result should be interpreted with caution given the modest difference seen in only one of the questionnaire scoring methods used. Our study sample size might have resulted in low power to detect differences for some outcomes (ie, type 2 error). For example, interpretation of hair cortisol results is limited by low sample size and a bias excluding most male participants whose hair tended to be too short to sample. The difference in school achievement seen in a previous follow-up,[13] not found in this study, is probably because many participants had finished school, allowing additional time for previously malnourished adolescents to catch up.

Despite some studies suggesting an association between childhood malnutrition and impaired glucose tolerance, evidence is inconclusive.[9] This question is particularly important in sub-Saharan Africa, where atypical diabetes in individuals with a low or healthy BMI and non-insulin-requiring diabetes are common, and previous malnutrition has been suggested as a potential underlying cause.[28] Our data do not support the hypothesis of previous childhood malnutrition substantially affecting long-term glucose tolerance or insulin sensitivity, although our sample size and timeframe do not exclude possible effects on these measures. We also did not find evidence of differences in blood pressure between exposed and unexposed groups

despite other studies indicating a potential association.[9] Therefore, additional research on cardiometabolic disease risk regarding the effect of the type of malnutrition (eg, oedematous malnutrition *vs* severe wasting), the food environment after malnutrition, and the risk in later life might be of use.[29]

A previous review found moderate evidence linking severe childhood malnutrition to cognitive impairment in later life.[12] The ChroSAM study found that previously malnourished children had lower cognition scores as measured by CANTAB than siblings and community children without previous severe malnutrition, but that differences diminished when adjusting for confounding variables.[13] We did not find strong evidence of differences in adolescence using the same methods despite previous research indicating that severe malnutrition impairs neurodevelopment in early childhood.[12] These results provide evidence of cognition in adolescent survivors at a level similar to unexposed peers.

Overall, this study contributes to the limited body of research on long-term outcomes of severe childhood malnutrition. We cannot rule out associations with long-term adverse outcomes due to participants still being relatively young, and our results do not detract from the need for an ongoing primary focus on preventing all severe childhood malnutrition, particularly given the severe negative consequences on development in early life.[12] However, our findings do suggest that although those who had severe childhood malnutrition might have persistently lower HAZ scores than those without previous severe malnutrition, there is optimism for survivors regarding ongoing catch-up growth and the recovery of strength deficits into adolescence. The first 1000 days of life is important, but so might be longer-term interventions in later childhood and adolescence to help individuals reach their full physical, developmental, cognitive, and social potential. Long-term follow-up of other cohorts across settings is needed to further understand the factors influencing recovery from known early-life impairments associated with severe malnutrition. Associated comorbidities and environmental factors that interact with severe childhood malnutrition and affect long-term outcomes also require additional investigation to optimise management after discharge. Practically, this management is likely to include associated comorbidities, such as HIV and disability, in addition to addressing environmental factors, such as the home environment, schooling, and poor socioeconomic conditions.

Contributors

AK, MK, MJG, BF, KM, and NL designed the study. AK, MK, MJG, KM, TC, and SL were involved in conducting the study. AK, PPH, OD, and AGJ were involved in data analysis. AK wrote the draft manuscript. AK and PPH had access to and verified the existence of the raw data. All authors were permitted to access the raw data. All authors had the final responsibility for the decision to submit the manuscript for publication. All study authors reviewed and contributed to the final submitted manuscript. The CHANGE study collaborators group were involved in advising on the conduct of the study and the interpretation of results.

Declaration of interests

We declare no competing interests.

Data sharing

Consent sought from participants included consent for anonymised data to be stored in a repository for future use and for use by other research groups. Anonymised data from this study will be uploaded to a secure online university repository within 6 months of publication. Data sharing for use in other analyses and studies can be sought via the corresponding author and the University of Liverpool (Liverpool, UK).

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References

1 WHO. Levels and trends in child malnutrition: UNICEF/WHO/The World Bank Group joint child malnutrition estimates: key findings of the 2021 edition. Geneva: World Health Organization, 2021.

2 Frison S, Checchi F, Kerac M. Omitting edema measurement: how much acute malnutrition are we missing? *Am J Clin Nutr* 2015; **102:** 1176–81.

3 Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013; **382:** 427–51.

4 Bwakura-Dangarembizi M, Dumbura C, Amadi B, et al. Risk factors for postdischarge mortality following hospitalization for severe acute malnutrition in Zimbabwe and Zambia. *Am J Clin Nutr* 2021; **113:** 665–74.

5 Briend A, Berkley JA. Long term health status of children recovering from severe acute malnutrition. *Lancet Glob Health* 2016; **4:** e590–91.

6 Kasonka L, Munthali G, Rehman AM, et al. Anthropometry, body composition and chronic disease risk factors among Zambian school-aged children who experienced severe malnutrition in early childhood. *Br J Nutr* 2022; **128:** 453–60.

7 Wells JCK. The capacity-load model of non-communicable disease risk: understanding the effects of child malnutrition, ethnicity and the social determinants of health. *Eur J Clin Nutr* 2018; **72:** 688–97.

8 Mwene-Batu P, Bisimwa G, Ngaboyeka G, et al. Severe acute malnutrition in childhood, chronic diseases, and human capital in adulthood in the Democratic Republic of Congo: the Lwiro Cohort Study. *Am J Clin Nutr* 2021; **114:** 70–79.

9 Grey K, Gonzales GB, Abera M, et al. Severe malnutrition or famine exposure in childhood and cardiometabolic non-communicable disease later in life: a systematic review. *BMJ Glob Health* 2021; **6:** e003161.

10 Lelijveld N, Seal A, Wells JC, et al. Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): a cohort study. *Lancet Glob Health* 2016; **4:** e654–62.

11 Grantham-McGregor S. A review of studies of the effect of severe malnutrition on mental development. *J Nutr* 1995; **125** (suppl): 2233S–38S.

12 Kirolos A, Goyheneix M, Kalmus Eliasz M, et al. Neurodevelopmental, cognitive, behavioural and mental health impairments following childhood malnutrition: a systematic review. *BMJ Glob Health* 2022; **7:** e009330.

13 Lelijveld N, Jalloh AA, Kampondeni SD, et al. Brain MRI and cognitive function seven years after surviving an episode of severe acute malnutrition in a cohort of Malawian children. *Public Health Nutr* 2019; **22:** 1406–14.

14 Leroy JL, Frongillo EA, Dewan P, Black MM, Waterland RA. Can children catch up from the consequences of undernourishment? Evidence from child linear growth, developmental epigenetics, and brain and neurocognitive development. *Adv Nutr* 2020; **11:** 1032–41.

15 Leroy JL, Ruel M, Habicht J-P, Frongillo EA. Linear growth deficit continues to accumulate beyond the first 1000 days in low- and middle-income countries: global evidence from 51 national surveys. *J Nutr* 2014; **144:** 1460–66.

16 Wrottesley SV, Lamper C, Pisa PT. Review of the importance of nutrition during the first 1000 days: maternal nutritional status and its associations with fetal growth and birth, neonatal and infant outcomes among African women. *J Dev Orig Health Dis* 2016; **7:** 144–62.

17 Scaling Up Nutrition. The SUN Movement Pool Fund. https://scalingupnutrition.org/sun-pooled-fund/about (accessed July 2, 2023).

18 Kerac M, Bunn J, Seal A, et al. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. *Lancet* 2009; **374:** 136–44.

19 Kerac M, Bunn J, Chagaluka G, et al. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM study): a prospective cohort study. *PLoS One* 2014; **9:** e96030.

20 The DHS Program. Wealth index construction. Nov 20, 2015. https://dhsprogram.com/topics/wealth-index/Wealth-Index-Construction.cfm (accessed July 2, 2023).

21 Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books, 1988.

22 de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. Food Nutr Bull 2004; **25** (suppl)**:** 15–26.

23 Koumantarou Malisiova E, Mourikis I, Chalimourdas T, et al. Low hair cortisol concentrations in obsessive compulsive disorder: a cross-sectional study. *J Psychiatr Res* 2020; **131:** 187–93.

24 Wells JC, Williams JE, Fewtrell M, Singhal A, Lucas A, Cole TJ. A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. *Int J Obes* 2007; **31:** 507–14.

25 Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian *J Endocrinol Metab* 2015; **19:** 160–64.

26 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; **22:** 1462–70.

27 Banapurmath CR, Prasad SM, Banapurmath S, Kesaree N. Follow-up study of survivors of severe protein energy manlnutrition. *Indian Pediatr* 1999; **36:** 139–43.

28 Bavuma C, Sahabandu D, Musafiri S, Danquah I, McQuillan R, Wild S. Atypical forms of diabetes mellitus in Africans and other non-European ethnic populations in low- and middle-income countries: a systematic literature review. *J Glob Health* 2019; **9:** 020401.

29 Francis-Emmanuel PM, Thompson DS, Barnett AT, et al. Glucose metabolism in adult survivors of severe acute malnutrition. *J Clin Endocrinol Metab* 2014; **99:** 2233–40.