

Severe acute malnutrition in childhood, chronic diseases, and human capital in adulthood in the Democratic Republic of Congo: the Lwiro Cohort Study

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ABSTRACT

Background: Little is known about the long-term outcome of children treated for severe acute malnutrition (SAM) after nutritional rehabilitation.

Objectives: To explore the association between SAM in childhood, noncommunicable diseases (NCDs), and low human capital in adulthood.

Methods: We identified 524 adults (median age: 22 y) who were treated for SAM during childhood in Eastern Democratic Republic of Congo between 1988 and 2007. They were compared with 407 community unexposed age- and sex-matched subjects with no history of SAM. The variables of interest were cardiometabolic risk markers for NCDs and human capital. For the comparison, we used linear and logistic regressions to estimate the association between SAM in childhood and the risk of NCDs and ordinal logistic regression for the human capital.

Results: Compared with unexposed subjects, the exposed participants had a higher waist circumference [1.2 (0.02, 2.3) cm; $P = 0.015$], and a larger waist-to-height ratio [0.01 (0.01, 0.02) cm; $P < 0.001$]. On the other hand, they had a smaller hip circumference [−1.5 (−2.6, −0.5) cm; $P = 0.021$]. Regarding cardiometabolic markers for NCDs, apart from a higher glycated hemoglobin (HbA1c) [0.4 (0.2, 0.6); $P < 0.001$], no difference was observed in other cardiometabolic markers for NCD between the 2 groups. Compared with unexposed participants, exposed participants had a higher risk of metabolic syndrome (crude OR: 2.35; 95% CI: 1.22, 4.54; $P = 0.010$) and visceral obesity [adjusted OR: 1.44 (1.09, 1.89); $P = 0.001$]. The prevalence of hypertension, diabetes, overweight, and dyslipidaemia was similar in both groups. Last, the proportion of malnutrition survivors with higher socioeconomic status level was lower.

Conclusion: SAM during childhood was associated with a high risk of NCDs and lower human capital in adulthood. Thus, policymakers and funders seeking to fight the global spread of NCDs in adults in low-resource settings should consider

the long-term benefit of reducing childhood SAM as a preventive measure to reduce the socioeconomic burden attributable to NCDs. *Am J Clin Nutr* 2021;114:70–79.

Keywords: long-term, childhood acute malnutrition, chronic diseases, follow-up, DR Congo

Introduction

Sub-Saharan Africa countries are experiencing a rapid health transition associated with a rapid rise in the prevalence of noncommunicable diseases (NCDs) and their risk factors, such as overweight and obesity in adults (1). The prevalence of overweight and obesity exceeds that of undernutrition (2). However, undernutrition still largely predominates among children in these regions (3).

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Abbreviations used: BP, blood pressure; CHW, community health worker; CM, chronic malnutrition; DBP, diastolic blood pressure; DM, diabetes mellitus; DRC, Democratic Republic of Congo; HbA1c, glycated hemoglobin; HMIC, high- and middle-income countries; HTA, hypertension; LIC, low-income countries; LPH, Lwiro Pediatric Hospital; MBP, mean blood pressure; MUAC, mid-upper arm circumference; NCD, noncommunicable disease; SAM, severe acute malnutrition; SBP, systolic blood pressure; SES, socioeconomic status; TG, triglyceride; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

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This growing prevalence of NCDs is partly driven by the nutrition transition (4). However, the role of episodes of undernutrition in the fetal period and in childhood is also increasingly recognized as a risk factor for the development of certain NCDs or for NCD risk factors in adulthood (5–8). This phenomenon, known as the “developmental origins of health and disease,” is well documented today (5). It has been studied mainly in high- and middle-income countries (HMICs) (5–8).

Despite growing evidence on the negative long-term effects of childhood undernutrition observed in HMICs, data related to the long-term outcomes of children treated for severe acute malnutrition (SAM) in low-income countries (LICs) are surprisingly scarce (9–11).

Studies conducted in Uganda and Malawi (LICs) showed that catch-up growth after an episode of SAM or delayed childhood growth, respectively, was associated with increased blood pressure (BP) in adolescence (11), and that prepubescent survivors of childhood SAM were at greater risk of subsequent NCDs, even though no clinical or biological marker was identified up to 7 y after nutritional rehabilitation (10).

While in South Kivu, located in the east region of the Democratic Republic of Congo (DRC), according to the report of the DRC National Nutrition Program (PRONANUT) published in 2019, half of all children younger than 5 y suffer from chronic malnutrition (CM) (12), available evidence indicates that the country is experiencing growing burdens of obesity, hypertension (HTA), diabetes mellitus (DM), metabolic syndrome, and abdominal obesity in both urban and rural settings (13, 14). However, the presumed role of childhood malnutrition in the increased burden of NCDs and related risk factors in the DRC has not been explored.

Our study investigated the long-term outcomes of childhood SAM on the health and human capital of a group of young adults screened 11–30 y after nutritional rehabilitation, with no nutrition transition (an environment with a monotonous, undiversified, and low-quality food situation), living in the east of the DRC. We primarily assessed the association between childhood SAM and NCD prevalence in adulthood based on different clinical and biological markers. We also documented the association between SAM in childhood and low socioeconomic status (SES) in adulthood.

Methods

Study design and population

The study was conducted among young adults who were treated for SAM during childhood at Lwiro Pediatric Hospital (LPH) between 1988 and 2007. At that time, diagnosis of SAM at LPH was based on the weight-for-height ratio plotted on the local child growth curve (established by DeMaeyer in 1959 and unpublished), the presence of nutritional edema, and low serum albumin concentrations (15, 16).

The nutritional status of the study subjects at the time of their admission to the hospital was reassessed in relation to the WHO child growth standard of 2006 (17). A new classification was established according to the following criteria.

Children were classified as having SAM if they met ≥ 1 of the following criteria: mid-upper arm circumference (MUAC) < 115 mm, weight-for-height z -score < -3 , and the presence

of nutritional edema in the hands and/or feet and/or face. Kwashiorkor was defined by the presence of nutritional edema in the hands and/or feet and/or face, MUAC > 115 mm, and weight-for-height z -score > -3 . Marasmus was defined by MUAC < 115 mm and/or weight-for-height z -score < -3 without nutritional edema. The mixed form was defined by the presence of nutritional edema with an MUAC < 115 mm and/or a weight-for-height z -score < -3 . Moderate acute malnutrition was defined by a weight-for-height z -score between -3 and -2 and/or an MUAC between 115 and 125 mm without nutritional edema. Last, CM was defined by a height-for-age z -score < -2 (17). The latter classification of nutritional status was used for the analyses in this study.

After a detailed analysis of the Nutrition Department archives for 1988–2007, a total of 2830 medical records of children admitted for SAM according to the criteria at that time were found and examined. Each record contained information on the subject's identity (name of child and parents, date of birth, sex, and health district of origin), vaccination schedule, anthropometric measurements (weight, height, and MUAC), serum albumin concentrations, physical examination on admission, nutritional diagnosis (marasmus, kwashiorkor, and marasmic kwashiorkor), treatment implemented, and status at discharge from the hospital.

The survey included participants with records containing the information cited above, who came from a health district in Miti-Murhesa or Katana and were ≥ 16 y old at the time of recruitment. The age of 16 was selected as the beginning of adulthood because most individuals are already pubescent at that age.

The exclusion criteria were records of patients who left or died during their hospital stay and those of patients transferred to another facility, along with records of adults admitted for SAM. Based on these criteria, of the 2830 records, 1981 records (70%) were selected for the study (18).

Over the course of 12 mo (December 2017 to November 2018), 20 community health workers (CHWs) and 2 supervisors worked full time, with the participation of community leaders, to trace individuals who had become adults (≥ 16 y old) and still living in Miti-Murhesa and Katana in the east of the DRC. Of the 1981 subjects who had been hospitalized, 1335 (67.4%) were traced and 646 (32.6%) were considered as lost to follow-up. Among those traced, 1134 subjects (84.9%) were still alive and 201 (15.1%) were deceased. Among those who were still alive, 600 (52.9%) were seen by the CHWs and 534 (47.1%) had moved to other regions. Of the 600 subjects seen, 524 agreed to participate in the study and 76 declined (Figure 1).

The malnutrition survivors who agreed to participate made up the exposed group. For each exposed subject, an unexposed community subject was randomly selected for comparison. An unexposed comparison subject was defined as a subject who had no hospital history of SAM, had the same sex, was living in the same community, and was ≤ 24 mo older or younger than the exposed subject. We selected community unexposed subjects randomly by spinning a bottle at the exposed adult's home and enquiring door to door, starting from the nearest house to where the bottle pointed (18).

However, unexposed subjects proved harder to recruit than exposed subjects, as many feared being associated with childhood malnutrition and its social stigma. Ultimately, we found unexposed subjects for 407 exposed subjects (18). Of the 524

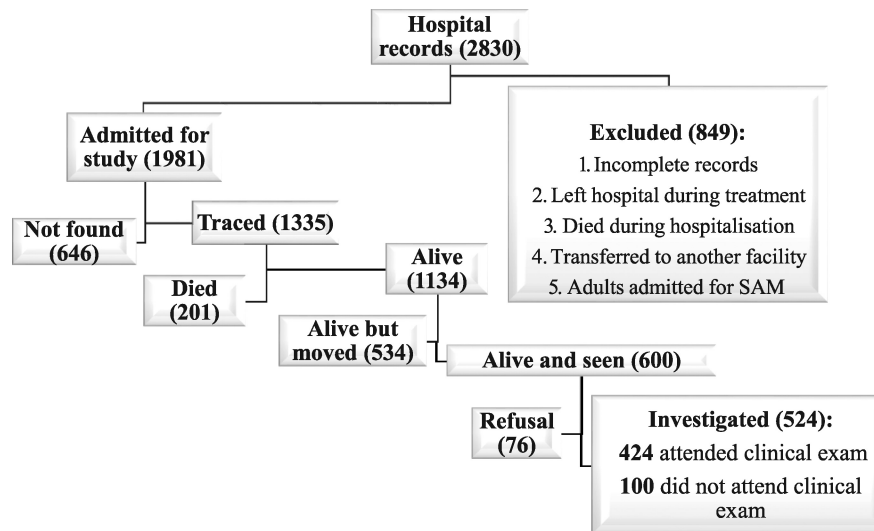


FIGURE 1 Recruitment of exposed group. SAM, severe acute malnutrition.

exposed and 407 unexposed subjects enrolled, 100 exposed and 85 unexposed subjects did not attend the appointments at the health facilities for the various clinical examinations, and for these we therefore only analyzed questionnaire data. Respondents provided signed informed consent for participation in the study, either by written signature or by fingerprints, depending on literacy. For children <18 y of age, consent was obtained from the children's parents or guardians.

Study framework

The study was conducted at the "Centre de Recherche en Science Naturelle de Lwiro (CRSN-Lwiro)," in the health zones of Katana and Miti-Murhesa in South Kivu, DRC. The Nutrition Department of this center has a pediatric hospital and 4 integrated health centers which monitor the state of the health and nutrition of children in the community (19).

Data collection

Data collection was carried out in 2 phases between August 2018 and December 2018 (5 mo). It was conducted by 20 trained CHWs and 2 supervisors and assisted by neighborhood leaders, licensed nurses, and community relays. The CHWs were the same as those who had helped identify the subjects during the creation of the cohort (18).

In the first phase home visits were performed. During these visits, the CHWs administered a questionnaire translated into Kiswahili to the participants, took their anthropometric measurements, and gave them an appointment, scheduled 24 to 48 h after their visit at the nearest hospital, for the second phase. This appointment involved venous and capillary blood samples and BP measurements taken by properly trained nurses working in the various health facilities in the 2 zones. Unlike the nurses and laboratory technicians who did not know whether a participant was an exposed or an unexposed, the CHWs knew this information.

The questionnaire covered variables relating to the participant's identity, their lifestyle (alcohol and tobacco consumption

as well as dietary habits), their medical history, and known cardiovascular risk factors (family or personal), as well as their socioeconomic status (education, occupation, and living conditions) (20).

The anthropometric measurements considered were weight, height, waist circumference, and hip circumference. Body weight was measured to the nearest 100 g using electronic scales (Tanita Digital HD-325®), with the subject wearing only light clothing. Height was determined to the nearest 0.1 cm using a SECA 206 cm® measuring device with the subject wearing no shoes. Waist circumference was measured to the nearest 0.1 cm using a measuring tape between the 12th rib and the iliac crest after a breath exhalation. For hip circumference, we used the same measuring tape with the 2 trochanters as a guide. The anthropometric measurements were carried out in accordance with WHO directives (17) and were quality controlled with 2 members of the team taking independent measurements. The final measurement was the average of the 2 independent measurements. In the event of a discrepancy between the independent measurements of >300 g for the weight, >0.5 cm for the height, or >1 cm for the waist and hip circumferences, a third measurement was taken. The average of the 2 closest measurements was used.

Muscle strength in kilograms was measured using a hand dynamometer (Takei Grip-D) twice for each hand (alternating). The participants carried out the test standing with their feet slightly apart, holding the dynamometer at thigh height, with the arm straight and held away from the body. They were asked to squeeze the dynamometer as hard as possible on an exhale. The highest values obtained for each hand were retained for the assessment of the muscle strength of the right and left hands. The maximum muscle strength corresponded to the highest value obtained, regardless of the hand.

BP was measured using an electronic device (OMRON Hem 7001E®). Three measurements were taken with the left arm held at heart level, at 5-min intervals, with the subject seated and relaxed for ≥ 5 min. The nurses used 1 of the 3 cuff sizes according to the size of each participant's arm. If the systolic blood pressure (SBP) or diastolic blood pressure (DBP)

measurements differed by >10 mm Hg, a fourth measurement was taken and the average of the 2 nearest measurements was used; otherwise, the average of the second and third measurements were used.

Capillary glycemia from finger-prick capillary blood sample was immediately analyzed by a glucose oxidase method using a portable electronic glucose meter (Code free®) with reactive strips that could be sourced locally. The method was calibrated in a hospital setting with a laboratory method prior to being implemented. Where fasting glycemia (last meal >8 h previously) or postprandial glycemia (last meal <8 h previously) were ≥ 126 mg/dL and ≥ 140 mg/dL, respectively, a fasting control test was carried out the following day.

Last, 4 mL of blood was taken using an antecubital venipuncture after 12 h of fasting to determine the lipid profile (HDL and LDL cholesterol, calculated according to the Friedewald equation (21), triglycerides (TG) and total cholesterol, glycated hemoglobin (HbA1c), and serum creatinine and albumin using standard calorimetric enzymatic methods (CYAN smart CY009) in the laboratory of the general provincial referral hospital in Bukavu (a tertiary hospital). HbA1c analysis was done in a subgroup of 116 subjects (58 exposed and 58 unexposed) due to limited financial means. Quality control of the blood analyses was performed using lyophilized human serum (normal and pathological control) by Cypress Diagnostics.

Outcomes

Our main outcomes of interest were NCDs, including, first and foremost, metabolic syndrome, hypertension, overall obesity, visceral obesity, DM, and dyslipidemia, assessed by their various clinical and biological markers, and second, serum creatinine. We assessed human capital defined by education, occupation, and SES in adulthood.

Dependent variables

Noncommunicable diseases.

Diabetes mellitus (DM) was defined as fasting glycemia ≥ 126 mg/dL and/or current treatment with hypoglycemic agents (22). Hypertension (HTA) was defined as a SBP ≥ 140 mm Hg and/or a DBP ≥ 90 mm Hg and/or current antihypertensive treatment. Mean blood pressure (MBP) was calculated using the formula: $MBP = DBP + 1/3 (SBP - DBP)$ (23).

BMI (in kg/m²) was grouped into 4 categories: <18.5, thinness; 18.5–24.9, normal; 25–29.9, overweight; and ≥ 30 , obese (24). Central obesity was defined by a waist circumference ≥ 94 cm for men and women (13, 25). Metabolic syndrome was defined as the presence of ≥ 3 of the 5 following risk factors: 1) central obesity (waist circumference ≥ 94 cm); 2) fasting hypertriglyceridemia (TGs ≥ 150 mg/dL or use of medication to reduce TGs); 3) low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women or use of medication to increase the concentration of HDL cholesterol) 4) hypertension (SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg and/or undergoing hypertensive treatment); 5) fasting glycemia ≥ 100 mg/dL or use of oral antidiabetic drugs (13, 26, 27). Visceral obesity was defined by a waist-to-height ratio (WHR) >0.5 (28). WHR and waist-to-hip ratio (WHR) were calculated by dividing the waist circumference (cm) by the height (cm) and the hip

circumference (cm), respectively. Dyslipidemia was defined by an LDL cholesterol concentration >200 mg/dL and/or an HDL cholesterol concentration <40 mg/dL (regardless of sex) (27). Last, muscle strength was measured with a Takei Grip-D device (Takei). A value of >16 kg for women and >26 kg for men was considered normal (29).

Socioeconomic level.

SES was established based on an empirical score taking into account the subject's level of education and occupation, as well as their living conditions. These living conditions were calculated based on the sum of material possessions owned (in 3 groups with the following ranges: 0–3 = few, 4–6 = average, and 7–9 = many), land ownership (yes/no), and type of housing in which the subject was living (with 3 categories: precarious, average, good) (30). The latter was defined on the basis of the components of the house (walls, roof, presence or otherwise of a cement floor in the house), the type of toilet, and the water supply (30). Good housing was considered for a house with walls made from durable or semidurable materials, a galvanized sheet metal roof, cement floor, inside fitted toilets and the presence of a tap on the plot of land. A home considered average housing had walls made from semidurable materials, a galvanized or recycled sheet metal roof, a cement floor, an outside toilet, and a water supply from a standpipe. Last, precarious housing was considered as a house with cob, plant, or clay walls, recycled sheet metal or thatched roof, no cement flooring, no toilet and a natural water source. The following material possessions were considered for each household: vehicle, motorbike, bike, computer, television, radio, telephone, bed made by a carpenter, and domestic animals (including ≥ 1 cow or 6 goats). The type of occupation was based on the "Classification Internationale Type des Professions," the French version of the International Standard Classification of Occupations adapted to the European Union (31). For this classification to apply appropriately in our context, we merged the first 3 occupation groups to give group 1 (manager). The groups 4 and 5 of the standard occupation classification became group 2 (administrative and office worker) and group 3 (farmer, fisher, market vendor), respectively. Last, groups 6 and 7 were merged into group 4 (unskilled workers). Unemployed subjects were put in group 4.

Based on all of this information, subjects were sorted into 3 SES categories. As such, we defined a subject with a low SES as any subject who had poor living conditions (precarious housing and owning few material possessions with or without land ownership), regardless of their occupation or level of education. Subjects with an average SES were those who had an occupation in groups 3 or 4, regardless of their level of education, and had good living conditions (good housing, a lot of material possessions, and owned land), or a subject who had average living conditions (had average housing, an average number of possessions, and owned land), and who also had a secondary level of education and an occupation in groups 2, 3, or 4. Last, a subject with a high SES had an occupation in groups 1 or 2, regardless of their level of education, and had good living conditions (had good housing and a lot of possessions and owned land), or a subject who had average living conditions, an occupation in group 1, and a university level education.

Independent variables

With regard to NCDs, primary exposure was a history of SAM during childhood. Other variables, such as age, sex, SES, anthropometric measurements in adulthood, lifestyle (alcohol, tobacco, and diet diversity), and family history of DM and/or HTA in the parents were added in the modeling as potential confounding factors.

Diet diversity was assessed using a dietary diversity score established by the WHO and the Food and Agriculture Organization of the United Nations (32–34). This score measures the dietary diversity of households, weighted according to frequency of consumption. To achieve this, we asked the head of the household (often the mother) how many days the household had eaten each of the following food groups in the last 7 days: grains, tubers, legumes, vegetables, fruit, meat/fish, milk/dairy products, sugar, oil/fat, and condiments. The frequency with which each food group was consumed was then multiplied by its nutritional value. Last, the scores for each food group were added to obtain the overall score. Depending on the total, the subject was considered as having an insufficient, borderline, or satisfactory diet if their score was 0–28, 28.5–42, or >42, respectively (34, 35). For tobacco exposure, a subject was considered as a smoker if he/she smoked at ≥ 1 cigarette (including hand-rolled cigarettes), a pipe, or other form of smoking tobacco regularly (>3 d/wk) (36). Last, for alcohol consumption, we considered any subject who consumed ≥ 2 standard glasses per day (women) or ≥ 3 glasses per day (men) of alcohol on a regular basis (>3 d/wk) (37).

Ethical standards

All procedures performed in this study were approved by the Institutional Ethics Committee of the Université Catholique de Bukavu and were in accordance with the 1964 Helsinki declaration and its later amendments.

Statistical analysis

We used the software Stata, version 13.1. The size of the sample was predetermined by the number of patients admitted for SAM at Lwiro pediatric hospital from 1998 to 2007 who were living in Miti-Murhesa and Katana in 2018, and who were identified as possible subjects and agreed to participate in our study. Categorical variables were summarized in the form of frequency and proportion. Quantitative data were presented as mean \pm SD or median and minimum to maximum (min-max), depending on whether the distribution was symmetrical.

Linear and logistic regression models were used, respectively, for the continuous variables (BMI, waist circumference, hip circumference, WHtR, and WHR), muscle strength, TGs, total cholesterol, HDL cholesterol, LDL cholesterol, HbA1c, fasting glycemia, albumin, creatinine, and BP (SBP, DBP, and MBP) and dichotomous variables (overall obesity, thinness, visceral obesity, DM, hypertension, metabolic syndrome and dyslipidemia). However, for the TGs, we made a logarithmic transformation given the usually asymmetrical nature of the distribution, and this variable was shown as geometric mean and dispersion interval. The basic models only included the primary exposure, SAM, giving a crude mean difference between the exposed and unexposed for the quantitative variables, and crude ORs for the

categorical variables. The mean differences and ORs are shown with 95% CIs. For the TGs, the exponential of the regression coefficient provided the geometric mean ratio.

Different models were then constructed to obtain adjusted effects of SAM. For each outcome, the adjustment variables were those significantly associated with the outcome and the exposition.

These different variables were chosen in models because nonmodifiable cardiovascular risk factors (gender, age, and parental history of HTA and/or DM) are obviously only predictive and are not predicted by other factors (38). Behavioral factors (alcohol consumption, dietary diversity, and smoking) form very few associations with each other, they predict many clinical factors and are predicted by a very small number of nonmodifiable or clinical factors (39, 38). Clinical factors (HTA, dyslipidemia, DM) form many associations with each other, they predict very few factors but are predicted by a large number of behavioral or nonmodifiable risk factors (38).

Last, ordinal logistic regression was used to analyze the differences between the exposed and their community unexposed as regards socioeconomic, education, and occupation variables and the dietary score. However, for the dichotomous variables, the Pearson chi-square test or Fisher exact test were used for comparison.

Results

Sociodemographic and economic characteristics of the population

The median age in the 2 groups was 22 y (min-max: 16, 40, 17–37, 39, 38), and males accounted for 52.1% and 50.6% of the exposed and unexposed, respectively. Compared with the unexposed, the exposed had a lower level of education, poorer housing, less land, and less satisfactory diet diversity. These differences were statistically significant (all $P < 0.05$). However, no significant difference was observed as regards material possessions or occupational categories (Table 1). The synthetic indicators for SES, constructed using the variables for living conditions, education, and occupation, were significantly better in the unexposed than in the exposed (Table 1).

Cardiometabolic markers and NCD prevalence in the 2 groups

The prevalence of overweight, DM, HTA, and metabolic syndrome were 13%; 9.6%; 6.5%; and 10.8% in the exposed and 12.9%; 7.5%; 6.4%; and 4.9% in the unexposed respectively. Last, the proportion of thinness was 7.7% and 3.8% in the exposed and unexposed respectively (Table 2).

Mean differences in clinical and biological markers for NCDs between exposed and unexposed

As shown in Table 3, in regard to anthropometry, compared with the unexposed, the exposed had a significantly higher waist circumference, WHR and WHtR. On the other hand, they exhibited significant lower hip circumference and smaller muscle strength than the unexposed. Importantly, these effects did not diminish after adjustment (for muscle strength).

TABLE 1 Sociodemographic and economic characteristics of the 2 groups of the study population

	Exposed		Unexposed		P value ²
	n (total)	Value ¹	n (total)	Value ¹	
Age, y	524	22 (16–40)	407	22 (16–40)	0.381
Male	524	52.1	407	50.6	0.351
Education level	515		405		
None		27.8		20.0	
Primary		37.1		33.6	<0.001
Secondary		34.2		42.0	
University		1.0		4.4	
Occupational category	479		359		
Executive		3.1		7.5	
Administrative + office worker		0.8		1.1	0.137
Farmer + fisher + market vendor		64.9		62.1	
Unskilled workers		31.1		29.3	
Living conditions					
A. Housing (wall + roof + cement floor + water + toilet)	524		407		
Precarious		33.4		21.1	
Average		63.5		74.4	<0.001
Good		3.1		4.4	
B. Material possessions (sum of all possessions)	524		407		
Few (≤ 3 possessions)		81.7		82.8	
Average (4–6 possessions)		18.1		17.2	0.848
Many (> 6 possessions)		0.2		0.0	
C. Land ownership (yes)	524	59.9	407	67.8	0.013
Socioeconomic status (education + living conditions + occupation)	472		357		
Low		64.0		55.5	
Average		33.1		37.8	0.007
High		3.0		6.7	
Diet diversity score	524		407		
Insufficient		11.1		6.9	
Borderline		39.3		31.7	<0.001
Satisfactory		49.6		61.4	

¹ Values are medians (minimum–maximum) or percentages unless otherwise indicated.

² P value calculated with ordinal logistic regression for ordinal variables.

As regards the different clinical and biological markers for NCDs (Table 3), the exposed had markedly significantly higher HbA1c than the unexposed, even after adjustment. However, BP (SBP, DBP, and MBP), lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and TGs), fasting glycemia, and creatinine were similar in the 2 groups, even after adjustment. Compared with unexposed, the exposed exhibited slightly lower concentrations of albumin; however, the observed difference diminished after adjustment.

Risk of developing NCDs in the exposed compared with the unexposed

Table 4 shows that, compared with the unexposed, the exposed had a significantly higher risk of visceral obesity, even after adjustment for confounders. The same effect can be seen for metabolic syndrome. No significant difference was observed for HTA, DM, overweight, and dyslipidemia. Of note, we observed that the exposed had a higher risk of thinness even after adjustment for diet diversity.

Discussion

Our findings suggest that SAM during childhood is associated with long-term negative effects on adult anthropometry and

muscle strength, but with lesser association on the development of overall obesity. In addition, it is associated with a high risk of NCDs in adulthood, mainly visceral obesity, metabolic syndrome and glucose homeostasis, even in a context of no nutrition transition. Importantly, SAM during childhood is associated with a lower SES than a general population with no history of childhood SAM.

A major finding of the present study was the high proportion of malnutrition survivors who developed visceral obesity indices (higher WHtR and WHR and a larger waist circumference), with a smaller hip circumference. This suggests an altered distribution between visceral adipose tissue and gluteo-femoral adipose tissue, and/or a gluteo-sarcopenia component. Our findings are consistent with those of other studies which reported that malnutrition survivors are at significantly higher risk of visceral obesity (8, 10, 41). This phenotype of individuals with central obesity puts them at risk of cardiometabolic events to a degree similar to or greater than obese or overweight subjects (42). Indeed, visceral fat is considered metabolically less favorable, particularly as regards the secretion of harmful adipokines. The presence of visceral fat positively correlates with an increased cardiometabolic risk, particularly atherosclerosis and the damaging effects of chronic insulin resistance and reactive hyperinsulinemia that the latter promotes (42–44).

TABLE 2 Cardiometabolic markers and NCD prevalence in the 2 groups¹

	Exposed			Unexposed			P value
	n (total)	%	Mean ± SD	n (total)	%	Mean ± SD	
Anthropometry							
Weight, kg	509		53.5 ± 7.9	396		55.1 ± 7.2	<0.001
Height, cm	520		155.9 ± 8.9	406		157.6 ± 8.9	0.002
BMI	509		22.0 ± 2.9	396		22.2 ± 2.5	0.24
Thinness		7.7			3.8		0.049
Normal		79.4			83.3		
Overweight		13.0			12.9		
Waist circumference, cm	519		79.1 ± 9.2	406		77.9 ± 8.3	0.046
Hip circumference, cm	517		84.5 ± 8.6	405		86.0 ± 7.7	0.005
Waist-to-hip ratio	516		0.94 ± 0.12	405		0.91 ± 0.11	<0.001
Waist-to-height ratio	519		0.51 ± 0.06	406		0.50 ± 0.06	0.001
Muscle strength, kg	385		29.9 ± 8.6	303		32.8 ± 8.8	<0.001
BP, mm Hg							
Systolic BP	358		121.1 ± 13.5	269		121.8 ± 12.9	0.54
Diastolic BP	386		70.9 ± 10.7			71.6 ± 10.1	0.37
Mean BP	358		95.8 ± 10.3			96.7 ± 9.8	0.29
Glucose							
Fasting glycemia, mg/dL	398		105.1 ± 16.5	319		103.7 ± 14.5	0.23
HbA1c, %	58		4.6 ± 0.6	52		4.2 ± 0.3	<0.001
Lipid profile, mg/dL							
Total cholesterol	424		154.2 ± 35.5	331		159.1 ± 36.6	0.062
HDL-C	424		43.8 ± 8.5	331		44.4 ± 8.4	0.37
LDL-C	412		90.1 ± 30.5	319		94.2 ± 31.2	0.08
TG	412		97.8 (74.7, 128.4) ²	322		97.2 (74.7, 126.4) ²	0.72
Creatinine, mg/dL	421		0.87 ± 0.17	331		0.88 ± 0.19	0.55
Albumin, mg/dL	424		4.38 ± 0.34	328		4.44 ± 0.31	0.020
Cardiovascular risk factors							
1. Alcohol (yes)	524	35.9		407	40.3		0.17
2. Tobacco (yes)	524	3.1		407	1.5		0.12
3. Parent with HTA and/or DM	524	32.3		407	32.9		0.83
4. Dyslipidemia							
High LDL-C	412	2.4		319	1.6		0.42
low HDL-C	424	38.4		331	34.1		0.22
5. DM	398	9.6		319	7.5		0.34
6. HTA	384	6.5		299	6.4		0.93
7. Visceral obesity	492	52.4		372	43.8		0.012
8. Metabolic syndrome	332	10.8		265	4.9		0.009
1. Central obesity	517	6.4		405	4.4		
2. Fasting hyperglycemia	398	32.4		319	25.4		
3. Low HDL-C	424	58.5		331	55.6		
4. High TG	412	8.7		322	7.1		
5. HTA or anti-hypertensive therapy	384	19.0		299	18.4		

¹BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HTA, hypertension; NCD, noncommunicable diseases; TG, triglyceride.

²Geometric mean ± SD.

Another important finding of the present survey is that malnutrition survivors had lower muscle strength in adulthood. These data are in keeping with previous observations in malnutrition survivors 7 y later after nutritional rehabilitation in Malawi (10). An initial hypothesis for this lower muscle strength could be that malnutrition survivors have reduced lean body mass in adulthood (45–47). Indeed, it has been shown that undernutrition in childhood is associated with a reduced lean body mass in adulthood independently of the potential catch-up growth that may have occurred afterward (8, 10). This might be due to the fact that after an episode of malnutrition, fat mass primarily accumulates in most parts of the body, which leads to a decrease in lean body mass in adulthood (45).

A reduced lean mass in adulthood is linked to lower thermogenesis, insulin resistance/hyperinsulinemia, decreased fasting and postprandial glucose uptake, raised risk of metabolic syndrome and/or type-2 diabetes, and higher incidence of atherothrombotic cardiovascular diseases (41, 42, 46).

As regards the risk of metabolic syndrome, we observed a higher prevalence in the malnutrition survivors than in the unexposed, which suggests increased insulin resistance and visceral obesity (Table 4). This observation is in line with those of other studies carried out in several regions of the world, which reported that subjects exposed to undernutrition in childhood were at greater risk of incident metabolic syndrome than those not exposed, with nearly similar ORs as those

TABLE 3 Mean differences (95% CI) in clinical and biological markers for NCDs between exposed and unexposed¹

	Crude difference (95% CI)	Adjusted difference (95% CI)
Anthropometry		
Waist circumference, cm (<i>n</i> = 925)	1.2 (0.02, 2.3)	
Hip circumference, cm (<i>n</i> = 922)	-1.5 (-2.6, -0.5)	
Waist-to-hip ratio (<i>n</i> = 921)	0.03 (0.02, 0.05)	
Waist-to-height ratio (<i>n</i> = 925)	0.01 (0.01, 0.02)	
Muscle strength, kg (<i>n</i> = 688)	-2.9 (-4.2, -1.6)	-3.0 (-4.3, -1.7) ^a
BP, mm Hg		
Systolic BP (<i>n</i> = 627)	-0.7 (-2.8, 1.4)	
Diastolic BP (<i>n</i> = 687)	-0.7 (-2.3, 0.9)	
Mean BP (<i>n</i> = 627)	-0.9 (-2.5, 0.7)	
Glucose		
Glycemia, mg/dL (<i>n</i> = 717)	1.4 (-0.9, 3.7)	1.1 (-1.3, 3.4) ^a
HbA1c, % (<i>n</i> = 110)	0.5 (0.3, 0.6)	0.4 (0.2, 0.6) ^a
Lipid profile, mg/dL		
Total cholesterol (<i>n</i> = 755)	-4.9 (-10.1, 0.3)	-3.8 (-9.3, 1.8) (<i>n</i> = 672) ^c
HDL-C (<i>n</i> = 755)	-0.6 (-1.8, 0.7)	-0.5 (-1.9, 0.8) (<i>n</i> = 672) ^c
LDL-C (<i>n</i> = 731)	-4.1 (-8.6, 0.4)	-2.8 (-7.6, 2.0) (<i>n</i> = 650) ^c
Triglyceride (<i>n</i> = 734)	1.01 (0.97, 1.04) ²	1.00 (0.97, 1.04) ^{2,a}
Creatinine, mg/dL (<i>n</i> = 752)	-0.01 (-0.03, 0.02)	
Albumin, mg/dL (<i>n</i> = 752)	-0.06 (-0.10, -0.01)	-0.04 (-0.09, 0.01) ^b (<i>n</i> = 669)

¹Difference with 95% CI calculated by linear regression. BP, blood pressure, HbA1c, glycated hemoglobin; NCD, noncommunicable diseases; SES, socioeconomic status.

²Geometric means ratio.

^aAdjusted for diet diversity.

^bAdjusted for SES.

^cAdjusted for diet diversity and SES.

observed in our study (OR: 2) (48–51). Malnutrition survivors generally have a low BMI during childhood so, in contrast to the unexposed population, it is possible that those who developed a metabolic syndrome had accelerated BMI gain after childhood, becoming “obese in relation to themselves” but without having a high BMI in absolute terms, which is consistent with the concept of “metabolically obese–normal weight” subjects (52). Consequently, the gain in BMI was based more on fat mass than on lean mass, in line with acquired insulin resistance and visceral obesity underlying the metabolic syndrome phenotype.

The exposed exhibited slightly higher HbA1c. This could probably expose them to a subsequent higher risk of glucose

homeostasis abnormalities in comparison to the unexposed. These glucose metabolism abnormalities could be ascribed to inadequate nutrition in childhood leading to decreased number or secretory function of pancreatic β cells, in addition to acquired insulin resistance in malnutrition survivors as a result of reduced lean body mass (53, 54). Another factor that may contribute to increased HbA1c is sarcopenia, which is associated with lower muscle glucose uptake, particularly in the postprandial period.

However, aside from HbA1c, other cardiometabolic markers for NCDs (BP, fasting glycemia, total cholesterol, LDL cholesterol, HDL cholesterol, and TG) were similar in both groups. Similarly, the frequencies of HTA, DM, low HDL cholesterol,

TABLE 4 Risk of developing NCDs (95% CI) in the exposed compared with the unexposed¹

	Crude OR (95% CI)	Adjusted OR
1. Dyslipidemia		
High LDL-C (<i>n</i> = 731)	1.56 (0.53, 4.62)	
Low HDL-C (<i>n</i> = 755)	1.20 (0.89, 1.63)	
High triglyceride (<i>n</i> = 734)	1.24 (0.72, 2.15)	
2. Diabetes (<i>n</i> = 717)		
3. Hypertension (<i>n</i> = 683)		
4. Visceral obesity (<i>n</i> = 864)		
5. BMI (<i>n</i> = 905)		
Overweight	1.06 (0.71, 1.57)	1.11 (0.75, 1.65) ^a
Thinness	2.12 (1.15, 3.92)	1.92 (1.03, 3.57) ^a
7. Metabolic syndrome (<i>n</i> = 597)		
	2.35 (1.22, 4.54)	

¹ORs (95% CIs) calculated by logistic regression. NCD, noncommunicable diseases; SES, socioeconomic status.

^aAdjusted for diet diversity.

^bAdjusted for SES.

and hypertriglyceridemia was comparable between the 2 groups. These findings are consistent with other studies conducted in low and middle-income countries (10, 41, 48, 49).

Last, we observed that, in contrast to unexposed, malnutrition survivors were less likely to achieve an education and a high SES, even after adjustment for age and gender, although no significant difference was observed as regards occupation. Our findings are consistent with those of several studies that show a strong link between undernutrition during childhood and reduced human capital later in life, pertaining to education, occupation, and social status (8, 55–57).

There are several limitations to this study. First, survivorship bias could represent a major limitation. Indeed, only 524 among 1981 subjects in the initial cohort were examined, and they could have had different characteristics than those of the subjects who were not studied. Nevertheless, we estimate that this would not be significantly different with regard to our main findings given that the characteristics on admission did not differ between those lost to follow-up and the subjects who were traced (18). Second, we do not have any infant health information, including gestational age, birth weight and height, or rate of growth in the first 2 y of life, nor on growth between the time of discharge from hospital and the time when our study was conducted. These variables are potential confounding factors because they are linked with both malnutrition and negative long-term effects (58). Third, although not malnourished in the past, the unexposed lived in the same unfavorable conditions as the exposed, and it is difficult to establish whether they were perfectly healthy on a cardiometabolic level. The continued unfavorable situation in which our 2 groups lived probably helped significantly reduce any differences in most cardiometabolic markers studied. Fourth, the study design is incapable of separating mechanisms due to SAM per se from mechanisms due to persistent effects of the child's early environment or persistent living in the same poor environment.

In conclusion, SAM during childhood is associated with a high potential risk of developing NCDs and a lower human capital in adulthood, even in the absence of nutrition transition.

These results underscore the relevance of implementing cost-effective strategies to prevent the onset of NCDs in adulthood and enhancing economic development through child nutrition improvement, BMI screening, and promotion of healthy lifestyle in later. Policymakers and funders seeking to fight the global NCDs epidemic in adults and to reduce poverty rates must be aware of the fact that appropriate investment in child health is a significant, albeit little known, means to improve adult health and economic development.

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the manuscript and agree with the manuscript's results and conclusions; and all authors: read and approved the final manuscript. Author disclosures: The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application to the corresponding author.

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