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Eleven to Thirty Years after: What happened to the Severely Malnourished Children hospitalized at Lwiro in the Eastern Democratic Republic of Congo?[1]

by

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Keywords. — Long Term; Childhood Acute Malnutrition; Chronic Diseases; Follow-up; DR Congo.
Summary. — The aim of this study was to trace subjects with a history of severe acute malnutrition (SAM) in childhood, to assess their long-term socioeconomic (SES) and health outcomes, and finally to investigate the different cardiometabolic markers of chronic non-communicable diseases (NCDs). Our results have shown that SAM childhood was associated with deleterious effects on anthropometry and body composition in adulthood (smaller weight, height, muscle strength and less fat free mass). In addition, adults with SAM history showed reduced human capital (reduced SES, self-esteem and cognition). However, with regard to the risk of NCDs, apart from an increased risk of visceral obesity, metabolic syndrome and glucose homeostasis, no additional risk was observed for other cardiometabolic markers of NCDs (blood pressure, fasting blood glucose and lipid profile) and risk of NCD occurrence (hypertension, diabetes mellitus, low HDL-C, and hypertriglyceridemia). Policymakers and donors involved in combating the global spread of NCDs in adults should consider the long-term benefit of reducing SAM in childhood as a preventive measure.

Mots-clés. — À long terme; Malnutrition infantile aiguë; Maladies chroniques; Suivi; RD Congo.
Résumé. — *Onze à trente ans plus tard: qu'est-il advenu des enfants souffrant de malnutrition sévère hospitalisés à Lwiro, dans l'est de la République Démocratique du Congo?* — L'objectif de cette étude était de retracer des sujets avec antécédents de malnutrition aiguë sévère (MAS) durant l'enfance, d'évaluer leur devenir à long terme sur le plan socio-économique et sanitaire, et enfin de rechercher les différents marqueurs cardiométaboliques des maladies chroniques non transmissibles (MNT). Il ressort de nos résultats que la MAS infantile est associée à des effets délétères sur l'anthropométrie et la composition corporelle à l'âge adulte (faible poids, petite taille, force musculaire et masse grasse libre réduites). En outre, les adultes avec antécédents de MAS présentent un capital humain réduit (statut socio-économique, estime de soi et cognition réduits). Toutefois, en ce qui concerne le risque de MNT, hormis un risque accru d'obésité viscérale, de syndrome métabolique et de troubles d'homéostasie du glucose, aucun risque supplémentaire n'a été observé au sujet d'autres marqueurs cardiométaboliques des MNT (pression artérielle, glycémie à jeun et profil lipidique) et de risque de survenue de MNT (hypertension,

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diabète sucré, faible taux de HDL-C et hypertriglycéridémie). Les décideurs politiques et les bailleurs de fonds impliqués dans la lutte contre l'expansion mondiale des MNT chez l'adulte devraient considérer le bénéfice à long terme de la réduction de la MAS chez l'enfant en tant que mesure préventive.

Background

Acute malnutrition (AM) is a public health problem in the world and particularly in low- and middle-income countries (LMICs) (FAO, FIDA, UNICEF, PAM & OMS, 2020). There are currently seventeen million children across the world suffering from severe acute malnutrition (SAM), of whom 27 % live in Africa. Each year, approximately seven million children under the age of five die worldwide and 45 % of these deaths are attributed to undernutrition (FAO *et al.*, 2020). The Sustainable Development Goals (SDGs) incorporated the World Health Assembly targets to reduce the proportion of children suffering from wasting to < 5 % by 2025 and < 3 % by 2030. However, since these targets were adopted, the proportion of wasted children has remained largely unchanged. In 2020, an estimated 7.3 % (fifty million) of all children under five are suffering from wasting at any given time (FAO *et al.*, 2020; Boero *et al.*, 2021).

Nevertheless, Sub-Saharan Africa (SSA), like most other LMICs, is undergoing a rapid epidemiological transition. In this region, there is a rapid increase in the prevalence of non-communicable diseases (NCDs) (diabetes, cardiovascular diseases, dyslipidemias, etc.) among adults, as well as their risk factors, notably overweight and obesity. The prevalence of overweight and obesity exceeds that of undernutrition (Caleyachetty *et al.*, 2018). In contrast, undernutrition still largely predominates among children in these regions (UNICEF, WHO & World Bank Group, 2017; Ng *et al.*, 2014; Caleyachetty *et al.*, 2018; Kimani-Murage, 2013; Hanandita & Tampubolon, 2015; Wells *et al.*, 2020). This well-documented phenomenon is known as the "double burden of malnutrition" and is a public health priority (Caleyachetty *et al.*, 2018).

The situation of wasting in the Democratic Republic of Congo (DRC) has been a cause for concern for the past decades. The DRC is one of the ten countries that account for 60 % of the global burden of wasting in children under five years of age. According to the Global Nutrition Report 2025, it is estimated that approximately 42.8 million people suffer from wasting globally, including 4.4 million children under five in the DRC (UNICEF, WHO & The World Bank, 2025). The DRC is one of the countries selected at global level to be part of the Global Action Plan on Child Wasting initiative, initiated by the United Nations General Secretariat.

In South Kivu, in the eastern part of the DRC, 7.9 % of all children under the age of five are suffering from AM (INS & MICS-Palu, 2019). The persistence of armed conflict over the past twenty years, limited accessibility of quality healthcare for the majority of the population, difficult access to farmland and inadequate nutrition are the main causes of this (Lindskog, 2016).

Lwiro paediatric hospital (LPH) was one of the first facilities to be involved in treating SAM in the DRC. A team of researchers developed a SAM treatment model in the 1980s and began digitizing clinical data in 1986. The electronic records contain sociodemographic, anthropometric, clinical and biological data gathered from inpatients between 1988 and 2007, from admission through to discharge from hospital. Even though the treatment programme has led to the recovery of most of the children, their medium- and long-term nutritional and health outcomes remain unknown.

In South Kivu, the prevalence of obesity, hypertension (HTA), diabetes mellitus (DM), metabolic syndrome (MetS) and abdominal obesity are 9.8 %, 19.0 %, 3.5 %, 7.2 % and 10.0 % respectively (Katchunga *et al.*, 2016). A recent study conducted in a rural area in this region has found a rising trend in the prevalence of HTA and obesity, as well as an increase in mean body mass index (BMI) and waist circumference (Katchunga *et al.*, 2019). However, the presumed role of SAM childhood in the increased NCD burden in the DRC has not yet been sufficiently examined, although suggested in several studies conducted in other regions with endemic childhood undernutrition.

This growing prevalence of NCDs is partly driven by the nutrition transition with changes in environmental factors impacting nutrition: urbanization, globalization, technological advances,... leading to a decrease in physical activity and a change in dietary behaviours with a higher consumption of processed products at the expense of traditional food, resulting in a higher intake of high glycemic index sugars, fat and salt (Wells *et al.*, 2020). However, the role of episodes of undernutrition in the foetal period and in childhood is also increasingly recognized as a risk factor for the development of certain NCDs or for risk factors of the latter in adulthood (Caleyachetty *et al.*, 2018; Wells *et al.*, 2020). This phenomenon, known as the "developmental origins of health and disease", is well documented today (Barker, 2004). It was especially studied in high- and middle-income countries (HMICs) (Victora *et al.*, 2008; Barker, 2004; Roseboom *et al.*, 2001). 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 SAM in low-income countries (LICs) are surprisingly scarce (Lelijveld *et al.*, 2016; Asiki, Newton, Marions, Kamali & Smedman, 2019).

In fact, studies conducted in Uganda and Malawi have shown that catch-up growth after an episode of SAM or delayed childhood growth, respectively, were associated with increased blood pressure (BP) in adolescence (Asiki *et al.*, 2019), and that pre-pubescent survivors of SAM childhood were at greater risk of subsequent NCDs, even though no clinical or biological marker of these subsequent morbidities was identified seven years after nutritional rehabilitation (Lelijveld *et al.*, 2016).

The aim of our study was to trace, eleven to thirty years after their nutritional rehabilitation, subjects with a history of SAM in childhood, to assess their long-term growth, socioeconomic and cognitive outcomes, and finally to investigate the different cardiometabolic markers of NCDs. All this was done in order to establish an association between SAM during childhood and different NCDs (hypertension, diabetes, obesity, dyslipidemias and body composition) as well as with sociodemographic and economic status in adulthood, in a context without nutritional transition.

Methodology

Study Framework

The study was conducted at the *Centre de Recherche en Sciences naturelles de Lwiro* (CRSN-Lwiro) in the health zones of Katana and Miti-Murhesa in South Kivu. The nutrition department of this centre has a paediatric hospital and four integrated health centres which monitor the state of the health and nutrition of children in the community (Paluku, 2002).

Study Design and Population

This is an observational follow-up study comparing young adults with a history of previous hospital admission for SAM with community controls. The study was conducted among young adults who were treated for SAM during childhood between 1988 and 2007 at LPH, South Kivu, DRC.

The nutritional status of the study subjects at the time of their admission to the hospital (Paluku, 2002) was reassessed in relation to the WHO child growth standard of 2006 (WHO Multicentre Growth Reference Study Group, 2006). 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 oedema in the hands and/or feet and/or face (WHO Multicentre Growth Reference Study Group, 2006).

Between December 2017 and April 2019, we set out to identify these subjects in the Miti-Murhesa and Katana health zones. Study subjects were identified from the LPH database. They were then traced to their home villages and afterwards divided into four categories (living in or near the village, deceased, displaced, or lost to follow-up) (Mwene-Batu *et al.*, 2020a,b, 2021a,b).

The malnutrition survivors (still alive and identified) who agreed to participate made up the exposed group. For each exposed, a community unexposed was randomly selected for comparison. An unexposed was defined as a subject who had no hospital history of SAM, had the same sex, was living in the same community, and was no more than twenty-four months older or younger than the exposed. We selected community unexposed randomly by spinning a bottle at the adult exposed's home and enquiring door to door, starting from the nearest house to where the bottle pointed (Mwene-Batu *et al.*, 2020a,b, 2021a,b). Though the optimal study design would be a 1:1 ratio of exposed and unexposed. However, unexposed participants proved harder to recruit than exposed ones, as many feared being associated with SAM childhood and its social stigma (Mwene-Batu *et al.*, 2020a,b, 2021a,b). For that reason, a ratio of 0.75 non-exposed per exposed was eventually achieved (Mwene-Batu *et al.*, 2020a,b, 2021a,b). Respondents provided signed informed consent for participation in the study, either by written signature or by fingerprints, depending on literacy. For children below eighteen years old, consent was obtained from their parents or guardians.

Data Collection

Data collection, from December 2017 to April 2019, was conducted in two phases with two stages each. It was carried out through the intervention of twenty trained community health workers (CHWs) and two supervisors and facilitated by neighbourhood leaders, licensed nurses and community relays.

The first phase focused on identification, sociodemographic data and the various clinical and biological markers of NCDs. The first stage concerned home visits. During these visits, the CHWs administered a questionnaire translated into Kiswahili to the participants, took their anthropometric measurements and gave them an appointment, scheduled twenty-four to forty-eight hours after their visit, at the nearest hospital for the second stage. This appointment involved venous and capillary blood samples and blood pressure (BP) measurements taken by properly trained nurses working in the various health facilities in the two zones.

The general questionnaire contained variables relating to the participant's identity, education, self-reported academic performance, cognitive function assessed using the MMSE and MMSE I tests, self-esteem (Rosenberg Self-Esteem Scale), and health-related daily functional and social disabilities. The final data concerned the frequency with which they listened to the radio and used social networks.

Due to copyright on the use of the MMSE and our limited means, we only used it in a subgroup of two hundred subjects (one hundred exposed and one hundred unexposed) (Newman & Feldman, 2011). HbA1c analysis was done in a subgroup of one hundred and sixteen subjects (fifty-eight exposed and fifty-eight unexposed) due to limited financial means (Mwene-Batu *et al.*, 2020a,b, 2021a,b).

The second phase involved the measurement of body composition. It was determined by the deuterium dilution method (D2O). Body composition was determined from the total body water (TBW). TBW was calculated from the saliva sample by the equilibration technique, assuming that the equilibration peak was reached at three to four hours after deuterium ingestion (IAEA, 2010). Fat free mass (FFM) was determined by dividing the participant's TBW by 0.732 (hydration factor for adults aged twenty-one or older). Fat mass (FM) was deduced from the difference between body weight and FFM. Curve fitting and calculation of results were performed using a spreadsheet model provided by the International Atomic Energy Agency (IAEA, 2013).

Outcomes

Our outcomes of interest were first and foremost NCDs including primarily metabolic syndrome, HTA, global obesity, visceral obesity, diabetes mellitus (DM), dyslipidemias as well as body composition (FFM, FM and TBW assessed by deuterium dilution method) assessed by their different clinical and biological markers (BMI, waist circumference, hip circumference, waist-to-height ratio (WHtR) and waist-to-hip ratio (WHR), muscle strength, triglyceride (TG), total cholesterol, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), glycated hemoglobin (HbA1c), FFM, FM, TBW, fasting glycemia, albumin, creatinine and blood pressure (systolic, diastolic and mean). The definition of different NCDs was based on international standard (American Diabetes Association, 2010; Mancia *et al.*, 2013; National Heart, Lung, and Blood Institute Obesity Education Initiative, 2000; Longo-Mbenza, Kasiam Lasi On'kin, Nge Okwe & Kangola Kabangu, 2011; Alberti *et al.*, 2009; National Cholesterol Education Program, 2002; Ashwell & Gibson, 2009; Celis-Morales *et al.*, 2018). Secondly, we evaluated the human capital through the socio-economic status (deduced from the education, the profession and the living conditions), self-esteem (measured using the French version of the Rosenberg Self-Esteem Scale – Schmitt & Allik, 2005) and the cognitive disorders assessed using the Mini-Mental State Examination (MMSE) (French consensual MMSE version – Derouesné *et al.*, 1999). Finally, we collected data on long-term nutritional status assessed by anthropometrics in adulthood.

Socio-economic status (SES) was established on the basis of an empirical score taking into account the subject's level of education and occupation, as well as living conditions (Mwene-Batu *et al.*, 2021a,b). These living conditions were calculated on the basis of the sum of material possessions owned, land ownership (yes/no) and type of housing in which the subject was living (with three categories: precarious, average, good) (Ministère du Plan de la R.D. Congo

& UNICEF, 2010). The latter was defined on the basis of house components (walls, roof, presence or otherwise of a cement floor in the house), type of toilet and water supply (Ministère du Plan de la R.D. Congo & UNICEF, 2010). 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 (Genoud, 2011). Based on all this information, subjects were sorted into three SES categories (low SES, average SES and high SES) (Mwene-Batu *et al.*, 2021a,b).

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 parents were added to the modelling as potential confounding factors (Mwene-Batu *et al.*, 2020a,b, 2021a,b). Diet diversity was assessed using a dietary diversity score established by the WHO and the Food and Agriculture Organization of the United Nations (IFPRI, 2014; WFP, 2008).

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 paediatric hospital from 1998 to 2007, living in Miti-Murhesa and Katana in 2018, who were found and agreed to participate in our study. Categorical variables were summarized in the form of frequency and proportion. Quantitative data were presented in the form of a mean and standard deviation (SD) or a median and minimum-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, TG, total cholesterol, HDL-C, LDL-C, HbA1c, FFM, FM, TBW, fasting glycemia, albumin, creatinine and blood pressure (systolic, diastolic and mean)] and dichotomous variables (overall obesity, thinness, visceral obesity, diabetes mellitus, hypertension, metabolic syndrome and dyslipidemia). However, for the TG, 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 primary exposure — SAM —, giving a crude mean difference between the exposed and unexposed for the quantitative variables, and crude odds ratios (OR) for the categorical variables. The mean differences and ORs are shown with confidence intervals of 95 % (95 % CI). For the TG, the exponential of the regression coefficient provides the geometric means ratio.

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

Lastly, ordinal logistic regression was used to analyse the differences between the exposed and their community unexposed with regard to socioeconomic, education and occupation variables and the dietary score. However, for the dichotomous variables, Pearson's Chi^2 test or Fisher exact test were used for comparison.

In all analyses, we considered a p value of 0.05 to show a statistically significant difference between the groups.

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.

Results

Recruitment of the Exposed Group

After a detailed analysis of the archives of the nutrition department of the CRSN for the period 1988 to 2007, a total of two thousand eight hundred and thirty medical records of children admitted for SAM, according to the criteria of the time, were retrieved and reviewed. After verification and on the basis of inclusion criteria, out of the two thousand eight hundred and thirty records obtained, only one thousand nine hundred and eighty-one records (70 %) were selected for the actual study. On admission to hospital, the median age was forty-one months, with 70.8 % of patients aged between six and fifty-nine months. There were more boys (57.5 %). Nearly three quarters of the patients were not up to date with their vaccination (Mwene-Batu *et al.*, 2020a,b).

Based on the WHO child growth standard, only 84 % of the children were classified as having SAM. The others were classified as having moderate acute malnutrition (6.7 %) and not suffering from AM (9.3 %). Nearly 90 % of the children admitted for SAM at the LPH also had stunting (Mwene-Batu *et al.*, 2020a,b).

Out of the one thousand nine hundred and eighty-one subjects hospitalized, one thousand three hundred and thirty-five (67.4 %) were traced and six hundred and forty-six (32.6 %) were lost to follow-up. Among those traced, one thousand one hundred and thirty-four subjects (84.9 %) were still alive and two hundred and one (15.1 %) were deceased. Among the living, six hundred (52.9 %) were seen by the CHWs and five hundred and thirty-four (47.1 %) had moved to other regions. Out of the six hundred subjects seen, five hundred and twenty-four agreed to participate in the study and seventy-six declined (Mwene-Batu *et al.*, 2020a,b).

Long-term Growth after Nutritional Rehabilitation (tab. 1)

The median age in the two groups was 22 (16-40), males accounted for 52.1 % and 50.6 % of the exposed and unexposed respectively. Compared to the unexposed, the exposed had significantly lower weight, shorter stature (sitting and standing), shorter leg length, and smaller brachial circumference. There were no significant differences in BMI, chest length, and head or chest circumference between the two groups (Mwene-Batu *et al.*, 2020a,b).

Adjusted Effect of Exposure on TBW (kg) and Fat Free Mass (kg)

As shown in table 2, compared to the unexposed, the SAM-exposed had a significantly lower TBW and FFM. Importantly, these effects did not diminish after adjustment (for sex, food diversity and age) (Mwene-Batu *et al.*, 2021a,b).

Sociodemographic and Economic Characteristics of the Population

Compared to the unexposed, the exposed had a lower level of education, poorer housing, less land, and less satisfactory diet diversity. These differences were statistically significant. However, no significant difference was observed with regard to material possessions or occupational categories (tab. 3). The synthetic indicator for SES, constructed by using the variables for living conditions, education and occupation, was significantly better in the unexposed than in the exposed group (tab. 3) (Mwene-Batu *et al.*, 2021a,b).

Academic Performance, Cognitive Function and Self-Esteem

Differences in terms of cognitive function and self-esteem between the exposed and the unexposed are shown in table 4.

Self-reported academic performance was also significantly lower in the exposed compared to the unexposed. By comparing the cognitive function of the two groups using the MMSE and MMSE-I (MMSE for illiteracies), we noted that the global mean scores were significantly lower in the exposed than in the unexposed (Mwene-Batu *et al.*, 2021a,b). The proportion of individuals who had a normal test was significantly lower in the exposed than in the unexposed. Overall, the exposed had statistically significant lower self-esteem than the unexposed. Lastly, compared to the unexposed, a significantly lower proportion of exposed regularly listened to the news on the radio or used social networks (Mwene-Batu *et al.*, 2021a,b).

Mean Differences in Clinical and Biological Markers for NCDs between Exposed and Unexposed

In terms of clinical and biological markers of NCDs, compared to the community unexposed, the malnourished elders had an increased waist circumference and a higher waist/standing height ratio. On the other hand, they had a decreased hip circumference and reduced muscle strength. Regarding cardiometabolic markers of NCDs, apart from a higher HbA1c, no differences were found in blood pressure (SBP, DBP and MBP), fasting blood glucose, creatinine, lipid profile (total cholesterol, LDL-C, HDL-C and TG) and albumin levels in the exposed compared to the unexposed (tab. 5) (Mwene-Batu *et al.*, 2021a,b).

Risk of Developing NCDs in the Exposed compared to the Unexposed

Compared to unexposed individuals, exposed individuals had an increased prevalence of metabolic syndrome, visceral obesity and thinness. In contrast, the prevalence of hypertension, diabetes, overweight and dyslipidemia was similar in both groups (tab. 6) (Mwene-Batu *et al.*, 2021a,b).

Table 1

Differences in long-term growth and anthropometry between exposed and unexposed (Mwene-Batu *et al.*, 2020a,b)

	All participants (931)	Exposed (524)		Unexposed (407)		Difference exposed-unexposed (95 % CI)	p value
	%	%	Mean (SD)	%	Mean (SD)		
Age (years) median (min.-max.)			22 (16-40)		22 (16-40)		
Male	51.4	52.7		49.8			
Weight (kg)			53.5 (7.9)		55.1 (7.2)	-1.7 (-2.6 to -0.6)	0.001
Height (cm)							
Sitting			112.6 (7.3)		113.9 (6.9)	-1.3 (-2.2 to -0.3)	0.006
Standing			155.9 (8.9)		157.6 (8.9)	-1.7 (-2.9 to -0.6)	0.003
Leg length			91.6 (7.3)		93.2 (8.6)	-1.6 (-2.6 to 0.5)	0.002
Thoracic length			44.6 (7.9)		44.9 (9.3)	-0.3 (-1.3 to 0.8)	0.64
BMI (kg/m^2)			22.1 (2.9)		22.2 (2.5)	-0.2 (-0.5 to 0.2)	0.29
< 18.5	5.9	7.5		3.8			
18.5-24.9	81.0	79.2		83.2			0.11
25-29.9	12.2	12.3		12.2			
≥ 30	0.9	1.0		0.8			
MUAC (mm)			253.5 (25.6)		256.6 (22.7)	-3.2 (-6.3 to 0.0)	0.051
Circumferences (cm)							
Head			54.9 (1.9)		55.1 (1.8)	-0.2 (-0.4 to 0.0)	0.07
Thoracic			83.5 (7.8)		83.9 (6.4)	-0.4 (-3.3 to 3.7)	0.29

Table 2

Adjusted effect of exposure on TBW (kg) and fat free mass (kg) (Mwene-Batu *et al.*, 2020a,b)

	TBW (kg)		Fat free mass (kg)	
Variable	**b (95 % CI)[1]**	**P**	**b (IC 95 % CI)[1]**	**P**
SAM **Exposed** **Unexposed**	 -1.13 (-2.12, -0.13) 0	0.027	 -1.56 (-2.93, -0.20) 0	0.024
Age (years)	0.10 (-0.01, 0.21)	0.062	0.17 (0.02, 0.31)	0.022
Sex Female Male	 -5.01 (-6.00, -4.02) 0	< 0.001	 -6.82 (-8.18, -5.47) 0	< 0.001
Food diversity Insufficient Satisfactory	 -0.80 (-1.80, 0.20) 0	0.118	 -1.04 (-2.41, 0.33) 0	0.136
	R^2: 0.28		R^2: 0.28	

[1] Difference with 95 % CI (confidence interval) calculated by linear regression.
b is the regression coefficient; TBW = total body water; SAM = severe acute malnutrition.

Table 3

Sociodemographic and economic characteristics of the two groups of the population study (Mwene-Batu *et al.*, 2021a,b)

	Exposed		Unexposed		p value[1]
	N (total)	%	N (total)	%	
LEVEL OF EDUCATION	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 worker		31.1		29.3	
Living conditions					
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 (at least three possessions)		81.7		82.8	
Average (four to six possessions)		18.1		17.2	0.848
Many (more than six possessions)		0.2		0.0	
C. Land ownership (yes)	524	59.9	407	67.8	0.013
SOCIO-ECONOMIC 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] p value calculated with ordinal logistic regression for ordinal variables.

Table 4

Difference in education, self-esteem and cognition between exposed and unexposed (Mwene-Batu *et al.*, 2021a,b)

	Exposed			Unexposed			p value[1]
	N (total)	%	Mean (SD)	N (total)	%	Mean (SD)	
EDUCATION							
1. Level of education	524			407			
None		27.8			20.0		
Primary		37.1			33.6		< 0.001
Secondary		34.2			42.0		
University		1.0			4.4		
2. SR academic performance	378			325			
Low		23.8			15.2		
Average		45.1			49.0		0.014
High		31.0			35.8		
COGNITION	100			100			
Mean MMSE score (SD)		50.0	25.6 (2.6)		72.0	27.8 (2.2)	0.001
Mean MMSE-I score (SD)		50.0	22.8 (2.1)		28.0	26.3 (2.9)	< 0.001
Normal		78.0			90.1		< 0.001
SELF-ESTEEM	518			405			
Low		20.5			12.1		
Average		72.6			78.5		0.003
High		6.9			9.4		
Listens to the news							
Listens to the radio news (yes)		40.0			49.2		0.007
Uses social networks		14.0			21.7		0.003

[1] p value calculated with ordinal logistic regression for ordinal variables.

Table 5

Mean differences (CI 95 %) in clinical and biological markers for NCDs between exposed and unexposed (Mwene-Batu *et al.*, 2021a,b)

	Crude difference (95 % CI)	Adjusted difference (95 % CI)
Anthropometry		
Waist circumference (cm) (n = 925)	1.2 (0.02, 2.3)	
Hip circumference (cm) (n = 922)	-1.5 (-2.6, -0.5)	
Waist-to-hip ratio (n = 921)	0.03 (0.02, 0.05)	
Waist-to-height ratio (n = 925)	0.01 (0.01, 0.02)	
Muscle strength (kg) (n = 688)	-2.9 (-4.2, -1.6)	-3.0 (-4.3, -1.7)[a]

Blood pressure (mm Hg)		
Systolic BP (n = 627)	-0.7 (-2.8, 1.4)	
Diastolic BP (n = 687)	-0.7 (-2.3, 0.9)	
Mean BP (n = 627)	-0.9 (-2.5, 0.7)	
Glucose		
Glycemia (mg/dL) (n = 717)	1.4 (-0.9, 3.7)	1.1 (-1.3, 3.4)[a]
HbA1c (%) (n = 110)	0.5 (0.3, 0.6)	0.4 (0.2, 0.6)[a]
Lipid profile (mg/dL)		
Total cholesterol (n = 755)	-4.9 (-10.1, 0.3)	-3.8 (-9.3, 1.8) (n = 672)[c]
HDL-C (n = 755)	-0.6 (-1.8, 0.7)	-0.5 (-1.9, 0.8) (n = 672)[c]
LDL-C (n = 731)	-4.1 (-8.6, 0.4)	-2.8 (-7.6, 2.0) (n = 650)[c]
Triglyceride (n = 734)	1.01 (0.97, 1.04)[1]	1.00 (0.97, 1.04)[1,a]
Creatinine (mg/dL) (n = 752)	-0.01 (-0.03, 0.02)	
Albumin (mg/dL) (n = 752)	-0.06 (-0.10, -0.01)	-0.04 (-0.09, 0.01)[b] (n = 669)

Difference with 95 % CI (confidence interval) calculated by linear regression. BP = blood pressure.
[1] Geometric means ratio.
[a] Adjusted for diet diversity.
[b] Adjusted for SES.
[c] Adjusted for diet diversity and SES.

Table 6

Risk of developing NCDs (95 % CI) in the exposed compared with the unexposed (Mwene-Batu *et al.*, 2021a,b)

	Crude OR (95 % CI)	Adjusted OR
1. Dyslipidaemia		
High LDL-C (n = 731)	1.56 (0.53, 4.62)	
Low HDL-C (n = 755)	1.20 (0.89, 1.63)	
High triglyceride (n = 734)	1.24 (0.72, 2.15)	
2. Diabetes (n = 717)	1.30 (0.76, 2.21)	
3. Hypertension (n = 683)	1.03 (0.55, 1.90)	0.98 (0.52, 1.85)[b] (n = 613)
4. Visceral obesity (n = 864)	1.41 (1.08, 1.85)	1.44 (1.09, 1.89)[a]
5. BMI (n = 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 (n = 597)	2.35 (1.22, 4.54)	

Odds ratio (OR) with 95 % CI (confidence interval) calculated by logistic regression.
[a] Adjusted for diet diversity.
[b] Adjusted for SES.

Discussion

Our findings suggest that SAM childhood has persistent deleterious effects on growth in adulthood. Moreover, it exposes survivors to potential risk of NCD occurrence and reduced human capital in adulthood, even in a setting without nutritional transition.

However, regarding the risk of NCDs, apart from higher risk of visceral obesity, metabolic syndrome and glucose homeostasis, we didn't note any statistically significant difference in the two groups in terms of cardiometabolic markers of NCDs (blood pressure, fasting blood glucose, HDL-C and TG). In addition, no difference was observed in terms of risk of NCD occurrence (hypertension, diabetes mellitus, low HDL-C and hypertriglyceridemia). Our results are in contradiction with almost all studies from HICs (Barker, 2004; Roseboom *et al.*, 2001; Painter, Roseboom & Bleker, 2005; Ravelli, van Der Meulen, Osmond, Barker & Bleker, 1999; Ekamper, van Poppel, Stein, Bijwaard & Lumey, 2015) and agree with those of some studies conducted in LMICs (Lelijveld *et al.*, 2016; Moore, Halsall, Howarth, Poskitt & Prentice, 2001; Li *et al.*, 2010; Burger, Drummond & Sandstead, 1948; de Rooij *et al.*, 2006).

This discrepancy may be caused by several factors, including different ethnicities, since our subjects were all sub-Saharan Africans whereas the vast majority of HICs inhabitants are Caucasians. These ethnicity-related differences could be attributed in part to genetic (Wells, 2012) and environmental factors. As such, sub-Saharan populations are characterized as having different determinants for the development of HBP and metabolic handling of normal or excess salt intakes, which could have a confounding effect on the data observed.

Secondly, there were major differences in age between the populations. The majority of our subjects were young adults (mean age: twenty-two), unlike those in studies from HICs (median age: fifty) (Roseboom *et al.*, 2001; Painter *et al.*, 2005; Ravelli *et al.*, 1999; AlGhatrif *et al.*, 2013). This would also partly explain the absence of age effect on NCDs, given that the effects of natural ageing on NCDs become more apparent after the age of fifty (AlGhatrif *et al.*, 2013). As our population was still relatively young, and given that the risk of NCDs increases with age, an additional ten to twenty years of hindsight would be needed to likely increase NCDs prevalence in this population.

Thirdly, lifestyle and socio-economic status before and after exposure to the episode of undernutrition differ between the two regions. In contrast to the studies conducted in HICs, our subjects spent their childhood in precarious nutritional conditions before experiencing one or more episodes of SAM, and then continued to live in an unfavourable environment in terms of food quality and security, without nutrition transition. In HICs, famines occurred in populations that generally had a high socio-economic status and good health prior to the episode of famine, and rapidly recovered this status afterwards (Roseboom *et al.*, 2001; Painter *et al.*, 2005; de Rooij *et al.*, 2006) whereas our cohort remained relatively disadvantaged during and after the episode of SAM, and therefore unexposed to an obesogenic environment up to adulthood. As a rule, people in South Kivu have little access to processed and/or industrialized food. The population keeps on consuming local food, with reduced fat content and poor in refined carbohydrates. However, one cannot rule out that target organ damage could become more apparent once they are subsequently exposed over long periods to Western-style lifestyles promoting weight gain.

The fourth reason could be the life history period of exposure to undernutrition. Our subjects were exposed to SAM during childhood and not in utero, as was the case in the majority of HICs. In contrast to changes to organ structure and function during the intra-uterine period, which are only partially reversible (Barker, 2004), the majority of organs have already reached full developmental maturity during childhood, and the changes associated with SAM could be less permanent than those occurring during the rapid foetal growth period, reducing the long-term effects of SAM childhood compared with foetal malnutrition.

Lastly, the difference between the criteria for diagnosing undernutrition should be taken into consideration. In HICs, undernutrition was defined on the basis of a reduction in weight gain whereas, in our population, undernutrition was defined on the basis of weight-to-height ratio, mid-upper arm circumference and/or presence of nutritional oedema. In addition, more than 90 % of our subjects had delayed growth during childhood (Mwene-Batu *et al.*, 2020a,b). Consequently, the effect of weight gain could be different in children who gained weight and height in a balanced way compared to those who gained weight and BMI, but had delayed growth. All of these factors may explain the differences in the findings observed.

There are several limitations to this study. First, the survival bias should be emphasized, which appears to be a major limitation of this study. In fact, only five hundred and twenty-four of the one thousand nine hundred and eighty-one subjects in the original cohort were examined, and they might have different characteristics from those of the unanalysed subjects. Nevertheless, we believe that this would not have significantly altered our main findings because the hospital admission characteristics did not differ between lost and traced subjects (Mwene-Batu *et al.*, 2020a,b). Another possible bias is that subjects with good socio-economic status and higher risk of NCDs may have moved to Bukavu or other cities, which could also lead to an underestimation of the effects of SAM on the variables studied.

Secondly, we do not have early life health information, including gestational age, birth weight and height, growth rate during the first two years of life, and data on the evolution of subjects between hospital discharge and the conduct of this study. We also do not have any data on the social and physical environment during the childhood of our subjects (episodes of infectious diseases, especially diarrhoea, birth rank), nor any socio-economic data of the mothers (level of education and age at delivery). These variables could be potential confounders, as they are related to both malnutrition and long-term deleterious effects.

Thirdly, it is questionable whether all of the recruited non-exposed individuals were in good nutritional status. Although they did not present with kwashiorkor and were not treated for SAM, it is possible that some of them presented with MAM related to the unfavourable socio-economic conditions of the region, but did not result in hospitalization. This permanent unfavourable situation in which both groups evolved probably could have mitigated intergroup differences for most of the studied cardiometabolic markers.

Fourthly, the fact that our study is an observational one requires us to be very careful in terms of causality analysis. Apart from SAM exposure, other factors may be associated with the different events studied. These factors may have occurred before the SAM episode, notably during pregnancy or early childhood. They may also be related to the physical and social environment in which our subjects have lived since their discharge from the hospital.

Fifthly, in our study we had access to only one capillary (not venous) blood sample for blood glucose determination, and no oral glucose tolerance test was performed. In addition, BP was measured on a single day, with no post testing (although measurements were optimal). All of this could have altered the observed differences in either direction.

Sixthly, we used psychometric tests (MMSE and MMSE-I) that have not been validated in the Congolese population, especially their Kiswahili versions. Therefore, we do not know to what extent this impacted the quality of the results. Nevertheless, having used a rigorous approach with pre-tests and a pilot study to address possible cross-cultural biases in terms of misunderstanding or lack of clarity, we believe that the lack of validation did not substantially alter the relevance of our findings.

Furthermore, given that 90 % of our study participants suffered from stunting as children, it is not impossible that some of the observed outcomes are more related to stunting than to SAM. Nevertheless, given that one child in two in South Kivu suffers from stunting and that food consumption was precarious in both groups (more so in the exposed group), we believe that the stunting effect would have been distributed across both groups and would not have greatly influenced our findings.

In spite of the mentioned limitations and given that there is a real paradox between the high prevalence of SAM in LMICs and the lack of information in the scientific literature about the potential long-term consequences of SAM, this study provides original data to help increase knowledge in this area. Therefore, policymakers and funders seeking to combat the global expansion of NCDs in adults should consider the long-term benefit of reducing SAM in childhood as a preventive measure.

Lessons learned from the DRC Lwiro Cohort Study and Research Perspectives

What we can learn from this research is that improving the childhood nutritional environment, BMI control, and lifestyle in adulthood is important for the prevention of NCDs occurrence and economic development. In addition, there is a high medium-term morbidity and mortality even after nutritional rehabilitation. Policymakers and donors seeking to address the global epidemic of NCDs and to reduce poverty rates should be aware that appropriate investment in young children's health is an important and often overlooked means of reducing the burden of extreme poverty and the cost of care for NCDs and complex psycho-medico social disorders in adults.

In the light of this and our observations, certain research perspectives deserve to be considered:

- Initiating follow-up of this cohort (every five years) or other cohorts of the same profile around the world over a longer term to detect a possible increase in the incidence of NCDs during follow-up of older subjects.
- Studying the long-term effect of the different subtypes of childhood malnutrition (kwashiorkor, marasmus, mixed form, moderate acute malnutrition, stunting), age at exposure to SAM, and type of treatment during the SAM episode on adult outcomes. This perspective is justified on the one hand by the fact that it has been documented that the effects of undernutrition would depend on the age of its occurrence. On the other hand, it has been shown that the risk of NCDs would differ according to the subtype of SAM.

— Studying with a comparable methodology cohort originally or secondarily established in urban areas, where the nutritional transition is more present.
— Studying the intergenerational effect of SAM on the offspring of exposed women in our cohort.
— Studying with medical imaging (brain CT-scan, abdominal and cardiac ultrasound) the long-term effects of SAM on the development of specific organs such as the central nervous system, gastrointestinal tract, pancreas, liver, kidney and cardiovascular system. This will allow us to explain certain clinical and biological abnormalities observed in this cohort.
— Studying the impact of birth weight on the risk of NCDs in adulthood in our context.

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