Eleven to thirty years after: what happened to the severely malnourished children hospitalized at Lwiro in the Eastern of the Democratic Republic of Congo?

Key words: Long-term, childhood acute malnutrition, chronic diseases, follow-up, DR Congo

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Abstract

The objective of this study was to retrace 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 showed that childhood SAM 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 history of SAM showed reduced human capital (reduced SES, self-esteem and cognition). However, regarding the risk of NCDs, apart from increased risk of visceral obesity, metabolic syndrome and glucose homeostasis, no additional risk was observed in terms of others 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 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.

Résumé

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 cardio-métaboliques des maladies chroniques non transmissibles (MNT). Il ressort de nos résultats que la MAS infantile est associé 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 en termes d'autres marqueurs cardiométaboliques des MNT (pression artérielle, glycémie à jeun et profil lipidique) et de risque de survenue de MNT (hypertension, 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 dans l'enfance en tant que mesure préventive.

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Background

Acute malnutrition (AM) is a public health problem in the world and particularly in low- and middle-income countries (LMICs) [FAO et al. (2020)]. There are currently 17 million children across the world suffering from severe acute malnutrition (SAM), of whom 27% live in Africa (1). Each year, approximately 7 million children under the age of 5 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. Yet, since these targets were adopted, the proportion of wasted children has remained largely unchanged. In 2020, an estimated 7.3% (50 million) of all children under five suffer from wasting at any given time [FAO et al. (2020), Boero et al. (2021)].

However, 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 2017, Ng M et al. (2014), Caleyachetty et al. (2018), Kimani-murage 2013, Hanandita W and Tampubolon G (2015), Wells et al. (2019)]. 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 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 5 years of age. By 2022, an estimated 2.8 million people will be suffering from global AM, including 1.2 million children under the age of five in DRC (HRP, 2022). The DRC is one of the countries selected at the 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 suffer from AM [INS U and 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 pediatric 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 program 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 2016). A recent study conducted in a rural area in this region 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 2019). However, the presumed role of childhood SAM 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 behaviors with a higher consumption of processed products at the expense of traditional food, resulting in a higher intake of high glycemic

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index sugars, fat and salt [Wells et al. (2019)]. 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 risk factors of the latter in adulthood [Caleyachetty et al. (2018), Wells et al. (2019)]. This phenomenon, known as the 'Developmental origins of health and disease' is well documented today (Barker 2006). It was especially studied in high- and middle-income countries (HMICs) [Victora et al. (2008), Barker 2006, 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 et al. (2019)].

Indeed, Studies conducted in Uganda and Malawi showed 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 childhood SAM 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 objective of our study was to trace, 11 to 30 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 socio-demographic and economic status in adulthood, in a context without nutritional transition.

Methodology

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. 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 (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 edema in the hands and/or feet and/or face (WHO Multicentre Growth Reference Study Group 2006)

Between December 2017 and April 2019, we undertook 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. They were then divided into four categories (living in or near the village, deceased, displaced, or lost to follow-up) [Mwene-batu et al. (2020), Mwene-batu et al (2021)].

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 24 months older or younger than the exposed. We

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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. (2020), Mwene-batu et al (2021)]. Though the optimal study design would be a 1:1 ratio of exposed and unexposed. However, unexposed participants proved harder to recruit than exposed participants, as many feared being associated with childhood SAM and its social stigma[Mwene-batu et al. (2020), Mwene-batu et al (2021)]. For that reason, a ratio of 0.75 non-exposed per exposed was eventually achieved [Mwene-batu et al. (2020), Mwene-batu et al (2021)]. Respondents provided signed informed consent for participation in the study, either by written signature or by fingerprints, depending on literacy. For children below 18 years of age, consent was obtained from the children's 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 20 trained Community Health Workers (CHWs) and 2 supervisors and facilitated by neighborhood 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 24 to 48 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 [47,48] and our limited means, we only used it in a subgroup of 200 subjects (100 exposed and 100 unexposed) (ref). HbA1c analysis was done in a sub-group of 116 subjects (58 exposed and 58 unexposed) due to limited financial means [Mwene-batu et al. (2020), Mwene-batu et al (2021)].

The second phase involved the measurement of body composition. It was determined by the deuterium dilution method (D2O). The 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 2013). Fat Free Mass (FFM) was determined by dividing the participant's TBW by 0.732 (hydration factor for adults aged 21 years 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 primarily 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

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2010, Mancia 2013, National Heart, Lung, and Blood Institute Obesity Education Initiative 2000, Longo-mbenza et al. (2011), Alberti et al. (2009), National Cholesterol Education Program 2002, Ashwell and 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), the self-esteem [(measured using the French version of the Rosenberg Self-Esteem Scale (Schmitt 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.

Socioeconomic status (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 [Mwene-batu et al (2021)]. These living conditions were calculated based on 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 et UNICEF (2010)]. 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 [(Ministère du Plan de la R.D. Congo et 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 (2021)].

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 [Mwene-batu et al. (2020), Mwene-batu et al (2021)]. 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, WPF 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 pediatric 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 the 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 analyze the differences between the exposed and their community unexposed as regards socioeconomic, education, and occupation variables and the dietary

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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

Recruitments 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 2,830 medical records of children admitted for SAM according to the criteria of the time were retrieved and reviewed. After verification and based on inclusion criteria, out of 2,830 records obtained, only 1,981 records (70%) were selected for the study proper. On admission to hospital, the median age was 41 months, with 70·8% of patients aged between 6 and 59 months old. There were more boys (57·5%). Nearly three quarters of the patients were not up to date with their vaccinations [Mwene-batu et al. (2020)]

Based on the WHO child growth standard, only 84% of the children were classed as having SAM. The others were classed 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. (2020)].

Out of the 1,981 subjects hospitalized, 1,335 (67.4%) were traced and 646 (32.6%) were lost to follow-up. Among those traced, 1,134 subjects (84.9%) were still alive and 201 (15.1%) were deceased. Among the living, 600 (52.9%) were seen by the CHWs and 534 (47.1%) had moved to other regions. Out of the 600 subjects seen, 524 agreed to participate in the study and 76 declined [Mwene-batu et al. (2020)].

Long term growth after nutritional rehabilitation (table 1)
The median age in the two groups was 22 (16-40), and 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 2 groups [Mwene-batu et al. (2020)].

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. (2021)].

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 as regards to material possessions or occupational categories (table 3). The synthetic indicator for SES, constructed using the variables for living conditions, education and occupation was significantly better in the unexposed than in the exposed group (table 3) [Mwene-batu et al. (2021)].

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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. 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 compared to the unexposed [Mwene-batu et al. (2021)]. The proportion of individuals who had a normal test was significantly lower in the exposed compared to 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. (2021)].

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 (table 5) [Mwene-batu et al. (2021)].

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 (Table 6) [Mwene-batu et al. (2021)].

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Table 1. Differences in long term growth and anthropometry between exposed and unexposed [Mwene-batu et al. (2020)]

	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/m2)			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

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Table 2: adjusted effect of exposure on TBW (kg) and Fat Free Mass (kg) [Mwene-batu et al. (2020)]

Variable	TBW (kg) b (95% CI)[1]	P	Fat Free Mass (kg) b (IC95% CI)[1]	P
SAM		**0.027**		**0.024**
Exposed	**-1.13 (-2.12, -0.13)**		**-1.56 (-2.93, -0.20)**	
Unexposed	**0**		**0**	
Age (years)	0.10 (-0.01, 0.21)	0.062	0.17 (0.02, 0.31	0.022
Sex		<0.001		<0.001
Female	-5.01 (-6.00, -4.02)		-6.82 (-8.18, -5.47)	
Male	0		0	
Food diversity		0.118		0.136
Insufficient	-0.80 (-1.80, 0.20		-1.04 (-2.41, 0.33)	
Satisfactory	0		0	
	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

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Table 3. Sociodemographic and economic characteristics of the 2 groups of the study population [Mwene-batu et al. (2021)]

	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 workers		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 3 possessions)		81.7		82.8	
Average (4 to 6 possessions)		18.1		17.2	0.848
Many (more than 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]p value calculated with ordinal logistic regression for ordinal variables

[1]Work presented on 29 march 2022 at Académie Royale des sciences d'Outre-Mer

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Table 4. Difference in education, self-esteem and cognition between exposed and unexposed [Mwene-batu et al. (2021)]

	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

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Table 5. Mean differences (CI 95%) in clinical and biological markers for NCDs between exposed and unexposed [Mwene-batu et al. (2021)]

	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)[1a]
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

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Table 6. Risk of developing NCDs (95% CI) in the exposed compared with the unexposed [Mwene-batu et al. (2021)]

	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 childhood SAM 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 noted no statistically significant difference in the 2 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 2006, Roseboom et al. (2001), Painter et al. (2005), Ravelli et al. (1999), Ekamper et al. (2015)] and agree with those of some studies conducted in LMICs [Lelijveld et al. (2016), Moore et al. (2001), Li et al. (2010), Burger et al. (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 22 years), unlike those in studies from HICs (median age 50 years) [Roseboom et al. (2001), Painter et al. (2005), Ravelli et al. (1999), AlGhatrif et al. (2013)]). This would also partly explain the absence of effect of age on NCDs, given that the effects of natural ageing on NCDs become more apparent after the age of 50 years (AlGhatrif et al. (2013)]. As our population was still relatively young, and given that the risk of NCDs increases with age, an additional 10-20 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

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childhood in precarious nutritional conditions before experiencing one or more episodes of SAM, and then continued to live in an unfavorable 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 foods, with reduced fat content and poor in refined carbohydrates. However, one cannot rule out that target organs 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 the HICs. In contrast to changes to organ structure and function during the intra-uterine period, which are only partially reversible (Barker 2006), the majority of organs already reached full developmental maturity during the childhood, and the changes associated with SAM could be less permanent than those occurring during the rapid fetal growth period, reducing the long-term effects of childhood SAM compared with fetal malnutrition.

Lastly, the difference between the criteria for diagnosing undernutrition must be taken into consideration. In HICs, undernutrition was defined based on 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 the presence of nutritional edema. In addition, more than 90% of our subjects had delayed growth during childhood [Mwene-Batu et al. (2020)]. 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. Indeed, only 524 of the 1981 subjects in the original cohort were examined, and they might have different characteristics from those of the unanalyzed subjects. Nevertheless, we believe that this would not have significantly altered our main findings because the hospital admission characteristics did not differ between the lost and traced subjects [Mwene-Batu et al. (2020)]. Another possible bias is that subjects with good socioeconomic 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.

Second, 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 data on the social and physical environment during the childhood of our subjects [episodes of infectious diseases (especially diarrhea), birth rank, nor 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.

Third, 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 unfavorable socioeconomic conditions of the region, but did not result in hospitalization. This permanent unfavorable situation in which both groups evolved probably could have mitigated possible intergroup differences for most of the studied cardiometabolic markers.

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Fourth, the fact that our study is an observational study 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.

Fifth, 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 the measurements were optimal). All of this could have altered the observed differences in either direction.

Sixth, 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 in two children 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. Thus, 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 are 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 complex psycho-medico social disorders in adults and to reduce poverty rates must 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 light of this and based on our observations, certain research perspectives deserve to be considered.

First, the initiation of 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.

Second, to study 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.

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Third, to study with a comparable methodology cohort originally or secondarily established in urban areas, where the nutritional transition is more present.

Fourth, to study the intergenerational effect of SAM on the offspring of exposed women in our cohort.

Fifth, to study 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.

Finally, to study the impact of birth weight on the risk of NCDs in adulthood in our context.

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