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Associations of early childhood exposure to severe acute malnutrition and recovery with cardiometabolic risk markers in later childhood: 5-year prospective matched cohort study in Ethiopia

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

Abbreviations

APPA, average posterior probability assignment; BAZ, BMI-for-age z-score; BIC, Bayesian information criterion; CMAM, community-based management of acute malnutrition; DDT, deuterium dilution technique; DOHaD, Developmental Origins of Health and Disease; EPHI, Ethiopian Public Health Institute; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HAZ, height-for-age z-score; HOMA-IR, homeostatic model assessment for insulin resistance; IAEA, International Atomic Energy Agency; JUCAN, Jimma University Clinical and Nutrition Research Center; LCT, latent class trajectory, LMCs, low-income countries; LMICs, low- and middle-income countries; NCDs, non-communicable diseases; SAM, severe acute malnutrition; WAZ, weight-for-age z-score.

Abstract

Background: Impaired fetal and accelerated postnatal growth are associated with cardiometabolic disease. Few studies investigated how recovery from severe acute malnutrition (SAM) is associated with childhood cardiometabolic risk.

Objective: We evaluated cardiometabolic risk in SAM children treated through community-based management, relative to controls, 5-year post-recovery. Recognizing the heterogeneity of SAM case definitions and patterns of nutritional recovery, we also identified distinct BMI-for-age (BAZ) trajectories of SAM children in the first-year post-recovery and examined their associations with anthropometry, body composition and cardiometabolic risk markers 5-years later.

Design: A prospective cohort study in 2013 enrolled children aged 6-59 months, recovered from SAM (n=203), or non-wasted controls (n=202), in Jimma Zone, Ethiopia. Anthropometry, body composition and cardiometabolic markers were assessed 5-year post-recovery. Multiple linear regression models compared outcomes between SAM-recovered children and controls. We used latent class trajectory modelling to identify BAZ trajectories in the first-year post-recovery and compared these trajectory groups with controls.

Result: We traced 291 (71.9%) children (mean age 6.2 years) at 5-year follow-up. Overall, compared to controls, SAM-recovered children did not differ in cardiometabolic risk. We identified 4 BAZ trajectories among SAM-recovered children: "Increase" (74.6%), "Decrease" (11.0%), "Decrease-increase" (5.0%), and "Increase-decrease" (9.4%). Compared to controls, all BAZ trajectories except "Decrease-increase" had lower weight, height and fat-free mass index. Compared to controls, the "Decrease-increase" trajectory had lower glucose (-15.8 mg/dL; 95%CI: -31.2, -0.4), while the "Increase-decrease" trajectory had higher glucose (8.1 mg/dL; CI: -0.8, 16.9). Compared to controls, the "Decrease-increase" and "Decrease" trajectories had higher total-cholesterol (24.3 mg/dL; CI: -9.4, 58.4) and LDL-cholesterol (10.4 mg/dL; CI: -3.8, 24.7), respectively. The “Increase” trajectory had lowest cardiometabolic risk.

Conclusion: Both rapid BAZ increase and decrease during early post-recovery from SAM were associated with greater cardiometabolic risk 5-years later. The findings indicate the need to target post-recovery interventions to optimize healthy weight recovery.

Keywords: body composition, severe malnutrition, weight gain; malnutrition recovery, cardiometabolic risk marker, biomarkers, post-recovery, post malnutrition

Introduction

Childhood undernutrition and adult non-communicable diseases (NCDs) are key global health problems (1). Nutrition-related factors contribute to nearly 45% of all deaths in children aged under 5 years (2). Globally, severe wasting affects an estimated 13.6 million children under 5-years, of whom more than 75% live in low- and middle-income countries (LMICs) (3). In parallel, obesity-related NCDs are emerging as a leading cause of premature death among adults in these settings, with nearly 75% of all NCD deaths occurring in LMICs (4).

The emerging epidemic of NCDs is partly explained by the Developmental Origins of Health and Disease (DOHaD) hypothesis, linking prenatal malnutrition with increased later NCD risk (5,6). In addition, undernutrition in early childhood is increasingly recognized as a risk factor for later NCDs (7–13). According to the capacity-load model (14), childhood undernutrition followed by later overweight increases NCD risk by imposing a high metabolic load on a depleted capacity for homeostasis. Thus, double-duty actions that simultaneously address this 'double burden' of malnutrition must be implemented for policy solutions to be effective (12,15).

In DOHaD research, most studies have focused on birth weight, and have emphasized the association of lower birth weight with later NCD risk (16–18), though a few studies also address high birth weight (19,20). Although historical cohort analyses, of people born in the 1920-30s, also linked low weight at 1 or 2 years after birth with later NCD risk (16,17,21), most studies of post-natal growth have focused on the risks associated with excess weight gain (22,23). In high-income countries, rapid catch-up growth in undernourished infants is associated with elevated childhood NCD risk (24–27). However, data from low-income countries (LICs) are scarce (28,29), even though children with severe acute malnutrition (SAM) are treated for a short duration with high-calorie and high-fat therapeutic foods to promote rapid weight gain and prevent short-term mortality (30). Few studies have focused on exposure to SAM in early life and later cardiometabolic risk in LICs (9–11,31) and the results are inconsistent. Moreover, these studies were of SAM survivors who received inpatient treatment, and who likely had advanced metabolic dysfunction or a depleted capacity for homeostasis.

Information is scarce on the long-term association of exposure to SAM with cardiometabolic risk markers among children treated in community-based management of acute malnutrition (CMAM) programs. Such programs allow early identification and treatment before severe metabolic disturbance or depleted capacity for homeostasis is established. Acknowledging the heterogeneity of case definitions for SAM and the variability in weight gain during nutritional recovery, this variability may in turn be associated with cardiometabolic outcomes. Based on the capacity-load model (14), we hypothesized that children exposed to SAM and treatment have increased cardiometabolic risk, and that this applies in particular to children with the most severe malnutrition who experience the most rapid weight gain during post-recovery period. Therefore, the primary aim of our study was to evaluate cardiometabolic risk in children 5-years after exposure to SAM and treatment in a CMAM program, in comparison with control children. Secondly, among children recovered from SAM, we aimed to identify distinct trajectories of body mass index z-score (BAZ) in the first year post-recovery and examine their associations with cardiometabolic outcomes at 5-year post-recovery, in comparison with the same control children as used in our primary aim.

Methods

Study participants, setting, and design

A prospective cohort study among children aged 6-59 months discharged from CMAM program and matched control children was conducted in the rural population of Jimma Zone, southwest Ethiopia. The study cohort, established in September 2013, has previously been described in detail (32,33). In brief, according to the 2007 Ethiopian National SAM management guidelines used at the time (34), children aged 6-59 months were enrolled into the CMAM program if their mid-upper arm circumference (MUAC) was ≤ 11.0 cm. The discharge criteria were: MUAC >11 cm, weight gain of 20% from admission weight, and absence of edema and clinical stability for two consecutive weeks. After the children had successfully recovered in the CMAM program, they were eligible for enrollment into the study as children recovered from SAM. For each child recovered from SAM case, an age (± 3 months) and sex-matched neighbor was enrolled as a control. The control children had no history of an episode of acute malnutrition at the time of enrollment, according to the national guidelines (34). During initial cohort establishment, we aimed to recruit a sample size of 237 children in each group (474 total), to allow the detection of an 8.5% difference in the incidence of acute malnutrition (wasting) during the first-year post-recovery between children recovered from SAM and controls. The calculated sample size could not be reached due to operational and resource constraints, resulting in a total of 430 children were screened for eligibility. Among these, 405 were enrolled. Details of the number of children followed at different time points are described elsewhere (33). Children were initially followed through monthly home visits for the first-year post-recovery. The subsequent follow-up took place in 2018, 5-years after exiting CMAM, hereafter referred to as 5-year post-recovery follow-up. At this follow-up, all children enrolled into the initial cohort were eligible. Based on the experience of similar previous studies (35,36), we anticipated tracing at least 70% of enrolled children. From those traced, we randomly selected a sample of 100 children recovered from SAM and 100 controls for cardiometabolic risk assessment. This sample size is able to detect differences of magnitude 0.4 standard deviations in any outcome, with 80% power, p=0.05. Tracing was undertaken by research enumerators in collaboration with local health extension workers. Mothers or caregivers of all traced children were requested to participate. For those giving consent, child socio-demography and anthropometric data were collected at home, and they were then invited to attend a nearby health post for body composition assessment and blood sample collection the following day.

Household characteristics and anthropometric measurements

Data collection procedures during the first-year post-recovery follow-up are described in detail elsewhere (32,33). In brief, data on sociodemographic and household characteristics and monthly child anthropometry data were collected. Sociodemographic and household characteristics were collected through caregivers' interview. Weight and height were measured using standard WHO procedures and were subjected to quality control (37). Height was measured to the nearest 0.1 cm using a height board and weight was measured to the nearest 0.1 kg (SECA 874, Hamburg, Germany). Hip and waist circumference were measured using a rollfix-Hoechstmass tape to the nearest 0.1 cm. The same procedures and instruments used during the first-year data collection were used for anthropometry at the 5-year follow-up (37).

Body composition assessment at 5-year post-recovery

Body composition was assessed using the deuterium dilution technique (DDT) (38). The procedure was undertaken in children with empty bladders who had fasted overnight. Sample collectors observed each child to ensure fasting for at least 30 minutes before collecting the first (pre-dose) saliva sample, by administering a cotton wool ball. The saliva in the cotton ball was squeezed into the barrel of a 20 ml syringe using the plunger and then into a Nunc tube until at least 2 ml of saliva was collected. Subsequently, under supervision, participants drank a dose of deuterium-labeled water with a straw based on their weight category (6 g for 10-20 kg children, 10 g for 21-30 kg children, and 20 g for >30 kg children) after adding 50 ml drinking water in the dose container. A "post-dose" saliva sample was then collected 3 hours after the dosing. All saliva samples were stored at 4 °C until they arrived at the laboratory for storage at −20 °C before being transported to the Ethiopian Public Health Institute (EPHI) for analysis. Saliva sample collection and deuterium administration were done as per International Atomic Energy Agency (IAEA) protocol (38). Analysis was carried out with Fourier transform infrared spectroscopy (FTIR 8400S spectrophotometer, Shimadzu Kyoto, Japan) after calibration, as per IAEA protocols (38). Deuterium dilution space was adjusted for proton exchange by dividing by 1.044 (39). According to IAEA protocol, quality control procedures were applied to the measures of enrichment of deuterium required for the total body water measures and to the estimates of total body water (TBW) (38). TBW was converted to fat-free mass (FFM) using age- and sex-specific values for the hydration (38) and the child's weight was used to calculate fat mass (FM), and their indexes (FFMI, FMI) were obtained by dividing FFM and FM in kg by the child's height in cm squared (40). Outliers in body fat percentage were excluded from analysis (13 children with negative % body fat values). The average intra-assay coefficient of variation for DDT was 0.28%.

Cardiometabolic markers assessment at 5-year post-recovery

Five mL of venous blood was collected using the Serum Separator Tube by the vacutainer blood collection system from the children after fasting overnight. The blood samples were mixed with a clot activator by 5–6 gentle inversions and kept upright on a test tube rack for 30 minutes at room temperature, allowing the blood to clot before centrifugation. Subsequently, samples were centrifuged at 3000 rpm for 10 minutes and then transported to the Jimma University Clinical and

Nutrition Research Center (JUCAN) Laboratory with a cold chain system (4 °C – 8 °C) on the same day of collection. At the JUCAN Laboratory, specimens were kept for 30 minutes at room temperature, and serum was separated and transferred to 2 mL Nunc tubes in aliquots of 500 µL, before being stored at -80 °C. Finally, the serum samples were transported to the EPHI, Clinical Chemistry Department, for laboratory analysis. Serum samples were analyzed using module c501 of the Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) for total-cholesterol (mg/dL), HDL (mg/dL), LDL (mg/dL), triglyceride (mg/dL), glucose (mg/dL) and module e601 for insulin (µU/mL). To estimate insulin resistance we calculated the homeostatic model assessment (HOMA-IR) as insulin (µU/mL) x glucose (mg/dL)/ 405 (41). Data collectors were trained to ensure data quality. Two levels of internal quality control materials (PreciControl ClinChem Multi 1, ref. 05947626160, and PreciControl ClinChem Multi 2, ref. 05947774160 for lipid profile and glucose; PreciControl Universal, ref. 11731416190 for insulin) were analyzed during all analytical series. The National Clinical Chemistry Reference Laboratory participated in the external quality assurance program (Oneworld Accuracy) and is also accredited by the Ethiopia National Accreditation Office. In addition, well-trained and experienced laboratory professionals performed the analysis. Specimen collection, processing and analysis were coordinated and continuously supervised by senior researchers.

Blood pressure measurement at 5-year post-recovery

After the child had relaxed for 5 minutes, their systolic and diastolic blood pressure was measured in the sitting position using a blood pressure monitor with age-appropriate cuffs (Riester, Big Ben 118 round, CE0124). Measurements were done in duplicate and results averaged.

Study outcomes

The study outcomes were total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, insulin, glucose, HOMA-IR, and blood pressure at 5-year post-recovery; data related to anthropometry and body composition for the two groups has been reported previously (33). However, in this analysis we also compared children recovered from SAM BAZ trajectories in the first-year post-recovery with control children for weight, height, hip, and waist circumferences, fat-free mass index, fat mass index, and the same listed above biomarkers at 5-year post recovery.

Statistical analysis

Data entry and consistency checks were performed using EpiData version 3.2 (Odense, Denmark). Statistical analyses were conducted using STATA Software/MP, Version 18 (College Station, Texas 77845 USA). Data were summarized using mean (standard deviation [SD]), and median (interquartile range [IQR]) for continuous normally distributed and skew variables, respectively. Categorical variables were presented using frequencies (n) and percentages (%). Study outcomes were checked for normality of distribution using histograms and Q-Q plots of the outcomes and residual terms. If skewed, outcome variables were log-transformed before the regression analyses. The estimates for skewed variables were back-transformed and reported as percent difference. For 75 children with missing data for LDL-cholesterol due to a shortage of reagents at the time, we estimated values using the Friedewald equation (42).

As our primary aim was to evaluate the association of exposure to SAM and recovery (exposure variable) with cardiometabolic risk markers at 5-year post-recovery (outcome variables), we fitted multiple linear regression models. We ran 4 separate models for each outcome variable. Variables were chosen based on their established relevance in prior literature (10,43,44). Model 1 was unadjusted. Model 2 was adjusted for child's sex, birth order (firstborn, second born, or ≥ third born) and age (year) at the 5-year post-recovery follow-up. Model 3 was additionally adjusted for season at discharge (lean or harvest), household food security (no, mild, moderate, or severe food insecurity), and economic status at the time of enrollment into our study (poorest, poorer, middle, or richer). Model 4 was further adjusted for child's fat mass (kg) and height (cm) at 5-year post-recovery. Child BAZ at 5-year follow-up was treated as an outcome variable and not adjusted for in the regression analyses, as it was on the causal pathway between growth and the cardiometabolic risk markers.

As our secondary aim was to understand the association of different growth trajectories in post-recovery period with later cardiometabolic disease risk, potential heterogeneity in BAZ trajectories was analyzed using latent class trajectory (LCT) modelling (also termed latent growth mixture modelling) to identify subgroups of children with distinct trajectories of BAZ growth in the first year post-recovery (45). We ran a series of LCT models with various specifications of BAZ as a function of post-recovery time and a number of subgroups (classes). The best-fitting model according to our a priori criteria was obtained with a model specified with natural cubic splines with boundary knots at 0 and 360 days, and internal knots at 30, 120, 215, and 330 days. Selection of the model with the optimal number of classes was guided by the Bayesian information criterion (BIC) (the lower value the better), average posterior probability assignment (APPA) (should be >70% for each class), relative entropy value (interval from 0-1, where values closest to 1 show lowest classification uncertainty), and size of each class (should be > 5%) (46–48). We also used the *calc_lrt* function in the R-package *tidyLPA* (version 1.1.0) to run the Lo-Mendell-Rubin adjusted likelihood ratio test for determining the ideal number of classes. Moreover, the selection was based on the clinical relevance of the model to address the subsequent research question, with the class variable serving as the primary exposure to capture variability in body composition and cardiometabolic risk markers 5 years post-recovery. A summary of these model selection indicators for the 1- 5-class LCT models of BMI-for-age z-score is provided in **Supplementary Table 1**. A detailed description of the LCT modelling is presented in the **Supplementary Methods**. LCT modelling was done using R statistical software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). For each of the identified BAZ trajectories, we applied mixed-effects modelling to estimate the corresponding mean growth in height-for-age z-score (HAZ) and weight-for-age z-score (WAZ) from enrollment to the first-year post-recovery. The HAZ and WAZ as functions of time since enrollment were modelled separately and fitted with natural cubic splines with knot points at enrollment, 30, 120, 215, 330, and 365 days post-recovery. As a supplementary exploratory analysis, we also conducted LCT modelling in the control children to examine heterogeneity in their BAZ. For this analysis, we followed a similar analysis strategy as for the children recovered from SAM (see the general description in the supplementary methods). Furthermore, using multiple regression analysis, we examined the differences in anthropometry, body composition and cardiometabolic risk markers across the identified BAZ trajectories in the control children using the same 4 models as for the primary aim.

To evaluate the association of the identified BAZ trajectories (subgroups) in the first year post-recovery (exposure variable) with cardiometabolic markers at 5-year post-recovery (outcome variables), we fitted multiple linear regression models. We ran the same 4 models as for the primary aim. Furthermore, to see the association of BAZ trajectories in the first-year post-recovery for children recovered from SAM (exposure variable) with anthropometry and body composition at 5-year post-recovery (outcome variables), we fitted similar multiple linear regression models except model 4. We used the BAZ trajectory of control children, who were not exposed to acute malnutrition at the time of enrollment, and whose BAZ closely mirrored the average pattern in the

WHO child growth standard, as the reference group in the regression analyses. This allowed us to evaluate our hypothesis, that children exposed to SAM and treatment who experience fast weight gain at post-recovery period have increased cardiometabolic disease risk later in childhood.

Ethical clearance

Ethical clearance was obtained from Jimma University's ethical review board (IHRPGD/458/2018). Parents or caretakers of the study children provided informed written consent.

Results

Cohort profile and characteristics

From September 2013 to September 2014, 430 children aged 6 to 59 months were screened for eligibility, and 405 (n= 203 children recovered from SAM, n=202 controls) were enrolled into the study **(Supplementary Figure 1)**. Of these, 391 (96.5%) (n= 193 children recovered from SAM, n=198 controls) completed the 1-year follow-up, and 291 (71.9%) (n= 141 children recovered from SAM, n=150 controls) were traced and enrolled into the 5-year follow-up study. There were some missing data, in particular for LDL-cholesterol, as detailed in the table footnotes.

At enrollment, children in both groups had similar household economic status and access to drinking water and sanitation (**Table 1**). However, a higher percentage of children recovered from SAM group were residing in severely food insecure households (27.7%) compared to control children (9.2%) (*p*=0.001). As previously reported, there were no differences in most discharge characteristics of traced children compared with those lost to follow-up (33). However, the wealth index quartile was higher in traced control children compared with controls loss to follow-up. At the 5-year follow-up, traced children had mean (SD) age of 6.2 (1.2) years and there were no age or sex differences between children recovered from SAM and control children. However, children recovered from SAM were shorter and lighter than the controls (Table 1).

Cardiometabolic risk markers in children recovered from SAM compared with controls

At 5-year post-recovery follow up, compared to controls, children recovered from SAM did not show differences in their metabolic profile [adjusted differences (95% CI) for children recovered from SAM relative to controls: total-cholesterol= -4.7 mg/dL (-12.2, 2.8); HDL-cholesterol -0.1 mg/dL (-3.0, 2.9); LDL-cholesterol -5.1 mg/dL (-11.5, 1.2); triglycerides -2.7% (-14.1, 10.2); glucose 0.4 mg/dL (-3.0, 3.8); insulin 2.7% (-24.2, 39.2); HOMA-IR 4.5% (-21.1, 44.0); systolic blood pressure -0.2% (-0.1, 2.6) and diastolic blood pressure -0.1% (-3.3, 3.1)] (**Figure 1 and Supplementary Table 2**).

Latent BAZ trajectories among children recovered from SAM

A total of 201 children were included in the modelling of the BAZ trajectories **(Figure 2).** The children had their BAZ assessed a median of 13 (IQR 11–13) times during the first-year post-recovery follow-up, contributing a total of 2337 observations to LCT modelling. We identified 4 heterogeneous BAZ trajectories among children recovered from SAM from enrollment into our study to the first-year post-recovery: “Increase” (74.6%, n=150), “Decrease” (11.0%, n=22), “Decrease-increase” (5%, n=10), and “Increase-decrease” (9.4%, n=19) (Figure 2). The ability of the LCT modelling to discriminate between the identified trajectories was acceptable, with mean posterior probabilities of assigned group membership above 90% for all 4 trajectories and relative entropy of 0.88 (Supplementary Table 1 and **Supplementary Figure 2**)**.** On average, children in the “Increase” trajectory showed modest BAZ gain throughout the first-year post-recovery. The “Decrease” trajectory showed, on average, slow deterioration of BAZ which leveled off around 7-

month post-recovery, followed by slow catch-up until 1-year, resulting in a low BAZ. The "Decrease-increase" trajectory showed initial fast BAZ deceleration that leveled off at 4-month post-recovery and with rapid catch-up reaching to normal BAZ at 1-year post-recovery. The "Increase-decrease" trajectory showed initial fast BAZ gain reaching the peak at 4-month and progressively declining towards low BAZ at 1-year post-recovery.

Latent BAZ trajectories among control children

When conducting LCT modelling among the control children, as an exploratory supplementary analysis, we identified a 3-class model as the best fitting model (**Supplementary Table 3** and **Supplementary Figure 3**). In the subsequent multiple regression analyses, differences in cardiometabolic risk markers were close to zero, with wide confidence intervals, despite some anthropometric differences between the reference trajectory (class 3) and classes 1 and 2, respectively (**Supplementary Figures 4 and 5**). We therefore treated the control children as a single reference group when comparing anthropometry, body composition and cardiometabolic markers between the distinct BAZ trajectory groups of the children recovered from SAM and the control children.

Weight- and height-for-age z-scores trajectories among children recovered from SAM

Figure 3 illustrates how BAZ trajectory is shaped by interacting trajectories of weight and height. In the "Increase" BAZ trajectory, we saw a modest decline in HAZ and a modest increase in WAZ, which reflects a modest trade-off between weight and height, leading to a steady 0.5 (SD) increase in BAZ z-score. "Decrease-increase" trajectory: a large increase in HAZ of +1 (SD), co-occurring with a 0.5 (SD) drop in WAZ (i.e., a major trade-off between height and weight) followed by a big increase of +1 (SD) in WAZ and a more modest decrease of 0.4 (SD) in HAZ. These successive trade-offs between HAZ and WAZ first allowed recovery of height, as this group was much shorter at baseline than the other groups, and then recovery of weight. "Increase-decrease" trajectory: a rapid increase of over 1 (SD) in WAZ, without any trade-off with HAZ. So represents WAZ gain and hence BAZ gain, associated with this group being the thinnest at baseline. "Decrease" trajectory: Stable HAZ, but a decline of almost 1 (SD) in WAZ. These children thus lose BAZ without transferring any energy saving into height growth, but were also the tallest at baseline.

The background characteristics and anthropometric measures of children based on BAZ trajectory group memberships are presented in **Table 2**. At the time of enrollment in the study, we did not observe any differences in socio-economic variables between the 4 BAZ trajectory groups. At 5-year post-recovery follow-up, children in all BAZ trajectories were, on average, lighter and shorter than the WHO international growth standards. Children in the "Decrease-increase" trajectory were taller (HAZ) than the other groups. There was no age or sex difference between the BAZ trajectories at 5-year follow-up (Table 2).

Cardiometabolic risk markers in latent BAZ trajectories of children recovered from SAM compared with controls

Compared to controls, children in all SAM BAZ trajectory groups had lower crude mean values for weight, height, hip and waist circumferences, and FFMI; except the "Decrease-increase" group who were taller than controls **(Table 3).** Conversely, the "Decrease-increase" and "Decrease" trajectories had higher crude mean values for total-cholesterol and LDL-cholesterol than controls, respectively. Similarly, compared to controls, all BAZ trajectory groups had higher crude median values for triglycerides. The "Decrease-increase" trajectory had lower crude mean glucose than controls, while the "Increase-decrease" trajectory had higher crude mean glucose (Table 3).

In model 4, compared to controls, all BAZ trajectory groups except "Decrease-increase" had lower weight, FFMI, height and smaller waist and hip circumferences **(Figure 4 and Supplementary Table 4)**.

In the unadjusted model (model 1), compared to controls, the "Decrease-increase" trajectory had 75% (3.6, 195.6; p=0.037) higher triglycerides and total-cholesterol (β-coefficient 33.2 mg/dL (1.9, 64.3); p=0.038). Model 4 showed the same pattern, with the "Decrease-increase" trajectory having 55.9% (-11.2, 174.0; p=0.121) higher triglycerides and total-cholesterol (β-coefficient 24.3 mg/dL (-9.4, 58.4); p=0.160). Similarly, in model 1, the "Decrease" trajectory had higher LDL-cholesterol (β-coefficient 13.6 mg/dL (1.4, 25.7); p=0.028) than controls; in model 4, the association remained, with the "Decrease" trajectory having higher LDL-cholesterol (β-coefficient 10.4 mg/dL (-3.8, 24.7); p=0.149) than controls (**Figure 5** and Supplementary Table 4).

In model 1, compared to controls, the "Decrease-increase" trajectory had lower glucose (β-coefficient -10.4 mg/dL (-24.6, 3.8); p=0.151), while the "Increase-decrease" trajectory had higher glucose (β-coefficient 7.4 mg/dL (-0.9, 15.8); p=0.081). In model 4, similar results were observed, with the "Decrease-increase" trajectory having lower glucose (β-coefficient -15.8 mg/dL (-31.2, -0.4); p=0.045) than controls, while the "Increase-decrease" trajectory had higher glucose (β-coefficient 8.1 mg/dL (-0.8, 16.9); p=0.073) (Figure 5 and Supplementary Table 4).

Crucially, in model 4, the "Increase" BAZ trajectory group, comprising 75% of the children recovered from SAM, had lower total-cholesterol (β-coefficient -6.6 mg/dl (; 95% CI: -14.3, 1.2); p=0.096) and LDL-cholesterol (β-coefficient -7.1 mg/dl (-13.7, -0.6); p=0.032) compared to controls. In addition, children in this trajectory had comparable blood pressure and glucose homeostasis markers compared to controls. However, still they had deficits in height, weight, and fat-free mass index (Figure 4, 5, and Supplementary Table 4). As observed in figures 4 and 5, the 95%CI estimates for each four children recovered from SAM BAZ groups were wide because of the smaller sample size.

Discussion

We evaluated cardiometabolic risk markers of children 5-years after being exposed to and treated for SAM, in comparison with matched control children who had not experienced SAM. As previously reported (33), children recovered from SAM had a "small" phenotype and less lean mass, but their fat mass was comparable with controls at 5-year post-recovery. In the current study, they had no overall difference in cardiometabolic disease risk compared to controls. Among children recovered from SAM, however, 4 distinct BAZ trajectories were identified. Having 13 BAZ values in the first-year post-recovery allowed us to see the complexity of BAZ trajectory among children recovered from SAM. Rather than manifesting as a simple linear rise or fall, BAZ is a complex trajectory resulting from underlying weight and height growth dynamics that often indicate trade-offs, in turn shaped by phenotype at enrollment. The average BAZ trajectory of control children was in line with the WHO international growth reference, supporting their use as the reference group. Cardiometabolic risk markers were elevated in some BAZ trajectory groups relative to controls, moreover we found that BAZ trajectories that are favorable for one component of cardiometabolic risk may be unfavorable for another.

The lack of overall difference in cardiometabolic risk markers between children recovered from SAM and controls mirrors findings from previous studies in Malawi and Zambia (10,44).

The metabolic signatures linked to cardiometabolic disease risk we describe may become amplified as SAM survivors becomes older. Children recovered from SAM might be at risk of developing cardiometabolic diseases later in life, as indicated by their smaller hip circumference and lower fat-free mass compared to controls (49), similar to findings from others (50–55). This is supported by a recent systematic review of cardiometabolic risk after long-term follow-up of people who experienced childhood SAM (8). Our cohort of children recovered from SAM demonstrated a "thrifty growth" pattern (33), which is a risk factor for subsequent development of type 2 diabetes and the metabolic syndrome (56). In such "metabolically thrifty" individuals, faster weight gain in the plastic developmental period of early childhood could drive an additional risk for later cardiometabolic diseases (57).

To test this hypothesis in more detail, we undertook LCA and identified 4 different BAZ trajectories in the first-year post-recovery period. Compared to controls, we found that the "Increase-decrease", "Increase", and "Decrease" trajectories of children recovered from SAM were associated with deficits in height, weight, hip circumference and fat-free mass at 5-year post-recovery follow-up, traits associated with increased risk of metabolic syndrome (50,54).

The "Increase" BAZ trajectory, the largest group (75%) with modest BAZ growth, showed BAZ trajectory similar to the controls, and did not differ in cardiometabolic risk. In contrast, the remaining 25% of the population sub-divided into three smaller groups, and displayed varying associations with cardiometabolic risk markers as discussed below. These three groups may have greater disparity between metabolic capacity and load, and hence be more prone to elevated NCD risk. Therefore, the absence of an overall cardiometabolic risk difference may be explained by the larger group overshadowing these smaller subgroups.

Compared to controls, the "Increase-decrease" BAZ trajectory had higher blood glucose concentration at 5-year post-recovery. This group showed the fastest initial weight gain (+1 SD) up to 4-months post-recovery, without any trade-off with HAZ, likely because they were thinnest at enrollment. This rapid weight gain might indicate restoring their deficit in fat that occurred during their initial adaptation to malnutrition (58), and may explain why this group had the highest fat mass of all trajectories including controls, however they had the lowest fat-free mass at 5-year post-recovery. In addition, this group had higher insulin and HOMA-IR value than controls, as well as higher blood glucose concentration for age compared to European reference data (59). Taken together, these findings suggest higher risk of dysregulated glucose metabolism in the "Increase-decrease" group, and increased risk of developing type 2 diabetes. In contrast, a study among SAM survivors in Jamaica found that 1-year post-recovery weight gain was not associated with adult blood glucose or insulin (60). Reasons for the contrasting findings might be differences in the follow-up age, study design, setting, genetics, or life-course and intergenerational effects.

Conversely, the "Decrease-increase" trajectory group had lower blood glucose than controls. This group showed a large initial increase in HAZ of + 1 SD, co-occurring with a 0.5 SD drop in WAZ, followed by a big increase + 1 SD in WAZ and a more modest decrease of 0.4 SD in HAZ. The successive trade-offs between WAZ and HAZ allowed recovery in both height and weight, in turn restoring fat mass. Furthermore, this trajectory had lower mean blood glucose compared to European reference data (59), suggesting that this pattern of BAZ recovery does not increase the risk of impaired glucose metabolism. However, the group had higher total-cholesterol and triglyceride levels compared to both controls and European reference data (61). This finding, whereby patterns of BAZ growth that are favorable for one component of cardiometabolic risk are unfavorable for another, indicates potential trade-offs in terms of how different organs and tissue respond to BAZ dynamics during recovery (62).

The "Decrease" trajectory had higher LDL-cholesterol than controls. However, compared to European reference data (61), this group had slightly lower mean LDL-cholesterol. Therefore, higher LDL-cholesterol values in the "Decrease" trajectory may not suggest dyslipidemia; rather, the control children may have had relatively low values too (63).

The study had several strengths, including long-term follow up of children recovered from SAM and matched control children, a high tracing rate, and accurate body composition measurements. The study also used LCA modelling, a data-driven method to identify distinct growth patterns in the early post-recovery period using a median of 13 repeated measurements of weight and height. An advantage of this method is that it does not impose observations into predefined groups during a specific period of follow-up, which could potentially overlook the complex and dynamic trajectories of child growth following SAM. It should be acknowledged that LCT modelling reduces the dimensionality of longitudinal data into a small number of groups. Therefore, these latent trajectories should be viewed as approximations of more complex growth patterns, rather than exact representations of individual growth paths.

Among other study limitations, sample size was low for some outcomes, resulting in wide confidence intervals. For the 5-year follow-up study, we did not calculate sample size a priori to assess cardiometabolic risk markers, but rather aimed to trace 70% of our original cohort, which was designed to assess malnutrition immediately post-recovery. Based on final numbers, our study could detect differences in any outcome of 0.4 standard deviations, with 80% power, p=0.05. Smaller effects could not be detected with statistical significance. The SAM children were admitted using old criteria, so findings may not fully reflect children treated under current guidelines. Estimated values for LDL-cholesterol due to reagent shortage may have introduced error. The follow-up period might not have been long enough to identify variability in cardiometabolic risk. Further studies following a similar population into adolescence and/or adulthood are recommended.

In conclusion, children recovering from SAM through CMAM may experience longer-term cardiometabolic risks, suggesting the need to redesign treatment for optimal short- and long-term health outcomes. Future programs in LMICs should focus on children who have survived SAM episodes.

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The authors' responsibilities were as follows — TG, KS, EB and AA designed the research; GG, MA, YA, AA, FC, and MB conducted the research; JW, RW, TG, HF, MFO, KS, EB, MB, MA, YA, FC and AA* assisted with data interpretation and writing the manuscript; GG, AA* and RW carried out statistical analysis. GG wrote the paper. All authors reviewed and approved the final manuscript. * Alemayehu Argaw

Conflict of interest

All authors declare no competing interests.

Data sharing

Data described in the manuscript, codebook, and analytic code will be made available upon request.

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Table 1: Child and household characteristics

		Children recovered from SAM[1]	Control children[2]
Characteristics	N	Mean (±SD) or n (%)	Mean (±SD) or n (%)
Household characteristics at enrollment			
Wealth index	268		
Poorest		31 (23.1)	24(17.9)
Poorer		29 (21.7)	40 (29.8)
Middle		33 (24.6)	34 (25.4)
Richer		41 (30.6)	36 (26.9)
Food insecurity	291		
No		86 (61.0)	119 (78.8)
Mild		3 (2.1)	3 (2.0)
Moderate		13 (9.2)	15 (10.0)
Severe		39 (27.7)	14 (9.2)
Drinking water source	291		
Improved		126 (89.3)	137 (90.7)
Unimproved		15 (10.7)	14 (9.3)
Toilet facility	291		
Improved		68 (48.2)	76 (50.3)
Unimproved		73 (51.8)	75 (49.7)
Child characteristics at 5-year post-recovery			
Age (year)	291	6.2 ± 1.2	6.3 ± 1.2
Sex, Male	291	73 (51.8)	79 (52.3)
Birth order	279		
Firstborn		13 (9.8)	31 (21.4)
Second born		19 (14.3)	28 (19.3)
≥ Third born		101 (75.9)	86 (59.3)
Height (cm)	291	102.5 ± 7.3	107.5 ± 8.7
Weight (kg)	291	14.9 ± 2.4	16.6 ± 2.8
Hip circumference (cm)	280	51.3 ± 3.0	53.3 ± 3.3
Waist circumference (cm)	281	52.2 ± 3.1	53.2 ± 2.8
BMI (z-score)	291	14.1 ± 1.5	14.3 ± 1.5
HAZ (z-score)	279	-2.7 ± 1.2	-1.8 ± 1.2
WAZ (z-score)	278	-2.6 ± 1.1	-1.8 ± 1.1
BAZ (z-score)	248	-1.1 ± 1.2	-1.0 ± 1.2

Data are mean (±SD) for continuous unless noted otherwise and count (%) for categorical variables. [1]Children recovered from SAM= children recruited at recovery from treatment for severe acute malnutrition in 2013 and enrolled in our study. [2] Control children= non-wasted matched group recruited concurrently as the children recovered from SAM. N=sample size for each variable. Abbreviations: BAZ, body mass index-for-age z-score; BMI, body mass index; HAZ, height-for-age z-score; SAM, severe acute malnutrition; SD, standard deviation; WAZ, weight-for-age z-score.

Table 2: Child and household characteristics of children recovered from SAM[1] with their 4 class BAZ trajectories in the first-year post-recovery period

Characteristics	N	"Increase-decrease" Mean (±SD) or n (%)[2]	"Increase" Mean (±SD) or n (%)[2]	"Decrease" Mean (±SD) or n (%)[2]	"Decrease-increase" Mean (±SD) or n (%)[2]
Household characteristics at enrollment					
Wealth index					
Poorest		3 (17.6)	39 (27.7)	5 (25)	3 (30)
Poorer	188	6 (35.3)	29 (20.6)	5 (25)	0 (0)
Middle		5 (29.4)	36 (20.5)	4 (20)	3 (30)
Richer		3 (17.6)	37 (26.2)	6 (30)	4 (40)
Food insecurity					
No		7 (36.8)	90 (60)	13 (59)	6 (60)
Mild	201	0 (0)	6 (4)	0 (0)	0 (0)
Moderate		4 (21)	12 (8)	2 (9)	0 (0)
Severe		8 (42.2)	42 (28)	7 (32)	4 (40)
Drinking water source					
Improved		19 (100)	135 (90)	20 (90.9)	10 (100)
Unimproved	201	0 (0)	15 (10)	2 (9.1)	0 (0)
Toilet facility					
Improved	200	9 (50)	68 (45.3)	12 (54.6)	5 (50)
Unimproved		9 (50)	82 (54.7)	10 (45.4)	5 (50)
Child characteristics at 5-year post-recovery					
Age (year)	141	6.6 ± 1.2	6.1 ± 1.2	6.0 ± 1.2	6.6 ± 1.5
Sex, Male	141	10 (53)	79 (53)	11 (50)	6 (60)
Height (cm)	141	103.3 ± 10.3	102.2 ± 6.8	103.1 ± 7.3	108.6 ± 12.6

Weight (kg)	141	14.5 ± 3.3	14.9 ± 2.3	14.6 ± 2.0	16.0 ± 2.9
Hip circumference (cm)	141	50.5 ± 4.2	51.5 ± 2.9	49.9 ± 3.0	52. 5 ± 3.1
Waist circumference (cm)	141	51.7 ± 4.7	52.4 ± 3.1	51.0 ± 2.2	52.4 ± 1.4
BMI (kg/m^2)	141	13.5 ± 1.4	14.3 ± 1.5	13.7 ± 1.2	13.6 ± 1.3
HAZ (z-score)	132	-3.2 ± 1.3	-2.6± 1.1	-2.6 ±1.1	-2.1 ± 1.3
WAZ (z-score)	132	-3.3 ± 1.2	-2.4 ± 1.1	-2.7 ± 1.1	-2.3 ± 0.4
BAZ (z-score)	118	-1.6 ± 1.3	-0.9 ± 1.1	-1.4 ± 1.0	-1.4 ± 1.1

N=sample size for each variable. [1]Children recovered from SAM= children recruited at recovery from treatment for severe acute malnutrition in 2013 and enrolled in our study and identified 4 class BAZ trajectories in first year post-recovery period. [2]Data are mean (±SD) for continuous unless noted otherwise and count (%) for categorical variables. Abbreviations: BAZ, body mass index-for-age z-score; BMI, body mass index; HAZ, height-for-age z-score; SAM, severe acute malnutrition; SD, standard deviation; WAZ, weight-for-age z-score.

Table 3: Descriptive information on cardiometabolic markers at the 5-year post-recovery follow-up of control children and children recovered from SAM with their first-year post-recovery BAZ trajectories

	N	Control children[2]	BAZ trajectories in the first year post recovery in children recovered from SAM[1]			
			"Increase-decrease"	"Increase"	"Decrease"	"Decrease-increase"
Anthropometry						
Height (cm)	291	107.5 ± 8.7	103.2 ± 10.3	102.2 ± 6.8	103.1 ± 7.3	108.6 ± 12.5
Weight (kg)	291	16.6 ± 2.8	14.5 ± 3.3	14.9 ± 2.3	14.6 ± 2.0	16.0 ± 3.0
Waist circumference (cm)	279	53.2 ± 2.8	51.7 ± 4.8	52.4 ± 3.2	51.0 ± 2.8	52.4 ± 1.5
Hip circumference (cm)	278	53.4 ± 3.3	50.5 ± 4.2	51.5 ± 2.9	49.9 ± 3.0	52.5 ± 3.1
BAZ (kg/m^2)	291	14.3 ± 1.5	13.5 ± 1.4	14.3 ± 1.4	13.7 ± 1.3	13.6 ± 1.3
Body composition						
Fat-free mass index (kg/m^2)	201	13.2 ± 1.5	11.8 ± 1.8	12.5 ± 1.5	11.9 ± 1.4	12.1 ± 1.8
Fat mass index (kg/m^2)	201	2.5 ± 0.9	2.6 ± 0.5	2.3 ± 0.9	2.2 ± 0.9	2.5 ± 0.8
Lipids (fasting values)						
Total-cholesterol (mg/dL)	218	128.5 ± 20.9	127.4 ± 19.7	124.6 ± 23.5	136.8 ± 22.9	161.7 ± 38.5
HDL-cholesterol (mg/dL)	216	30.8 ± 8.7	26.4 ± 5.5	30.6 ± 9.5	31.1 ± 6.7	35.8 ± 15.7
LDL-cholesterol[3] (mg/dL)	210	66.2 ± 18.4	67.6 ± 15.6	61.7 ± 18.8	79.8 ± 20.7	80.6 ± 24.3
Triglycerides (mg/dL)	208	109.8 (87.2-140.7)	110.1 (109.0-140.5)	113.3 (83.7-152.2)	116.2 (96.9-138.8)	196.9 (192.5-201.3)
Glucose metabolism (fasting values)						
Glucose (mg/dL)	219	79.7 ± 9.5	87.2 ± 15.4	80.2 ± 10.7	81.5 ± 8.3	69.4 ± 11.4
Insulin (µU/ml)	111	9.0 (5.7-14.2)	16.1 (16.1-16.1)	8.5 (5.4-13.5)	9.2 (4.7-17.3)	10.0 (6.3-13.8)
HOMA-IR[4]	111	1.8 (1.1-2.8)	3.3 (3.3-3.3)	1.7 (1.0-2.8)	1.8 (0.9-3.0)	1.8 (1.0-2.6)
Blood pressure						

Systolic (mm Hg)	229	90 (80-90)	85 (80-90)	80 (80-90)	80 (80-90)	90(90-90)
Diastolic (mm Hg)	229	65 (60-75)	67 (60-70)	65 (60-70)	60 (60-70)	68 (65-70)

Data are mean (±SD) and median (IQR). [1]Children recovered from SAM= children recruited at recovery from treatment for severe acute malnutrition in 2013 and enrolled in our study and identified 4 class BAZ trajectories in 1-year post-recovery period. [2]Control children= non-wasted matched group recruited concurrently as the children recovered from SAM. N= sample size for each outcome variable.[3]LDL-cholestrol=For 75 children with missing data for LDL-cholesterol due to a shortage of reagents at the time, we estimated values using the Friedewald equation.[4]HOMA-IR was calculated as insulin (mg/dL) × glucose (mg/dL)/405. Abbreviations: BAZ, body mass index-for-age z-score; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; SAM, severe acute malnutrition.

Figures legend

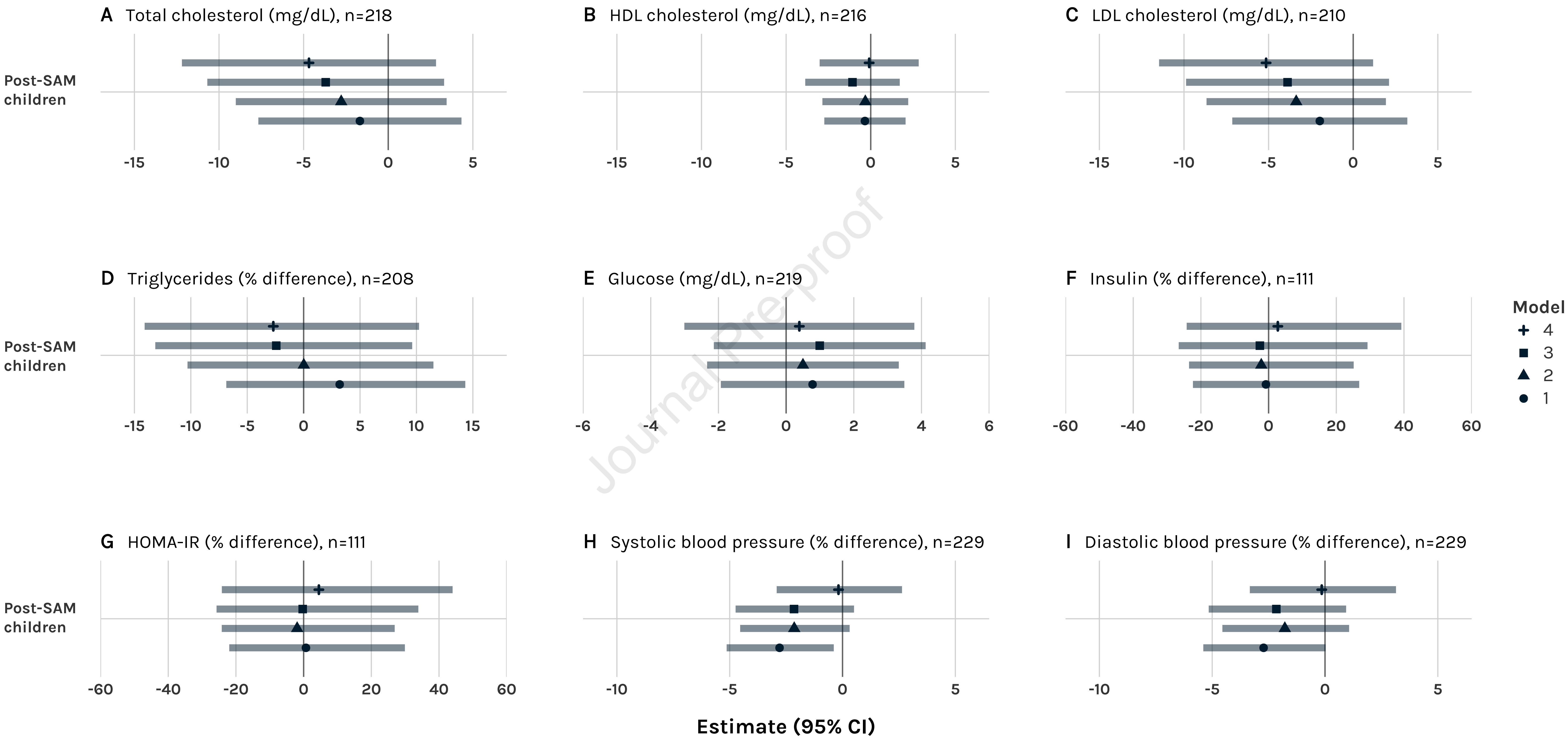
Figure 1: Forest plots showing the associations of early life exposure to and treatment of SAM with cardiometabolic risk markers at 5-year post-recovery, in comparison with control children. The coefficients are derived from separate multiple linear regression analyses and represent the mean difference between the control and the children recovered from SAM group. Variables found not to follow a normal distribution (i.e., insulin, triglyceride, HOMA-IR, and blood pressure) were log-transformed prior to the regression analyses. The presented estimates for these variables were backtransformed and shown as percentwise difference. Model 1 was unadjusted. Model 2 was adjusted for child's sex, birth order (firstborn, second born, or ≥ third born) and child's age (year) at the 5-year follow-up. Model 3 was additionally adjusted for season at discharge (lean or harvest), household food security (no, mild, moderate, or severe food insecurity) and economic status at the time of enrollment to our study (poorest, poorer, middle, or richer). Model 4 was additionally adjusted for fat mass (kg) and height (cm) at the 5-year follow-up. The X-axis represent the estimate with 95% confidence interval and Y-axis shows the difference of the children recovered from SAM compared to control children.

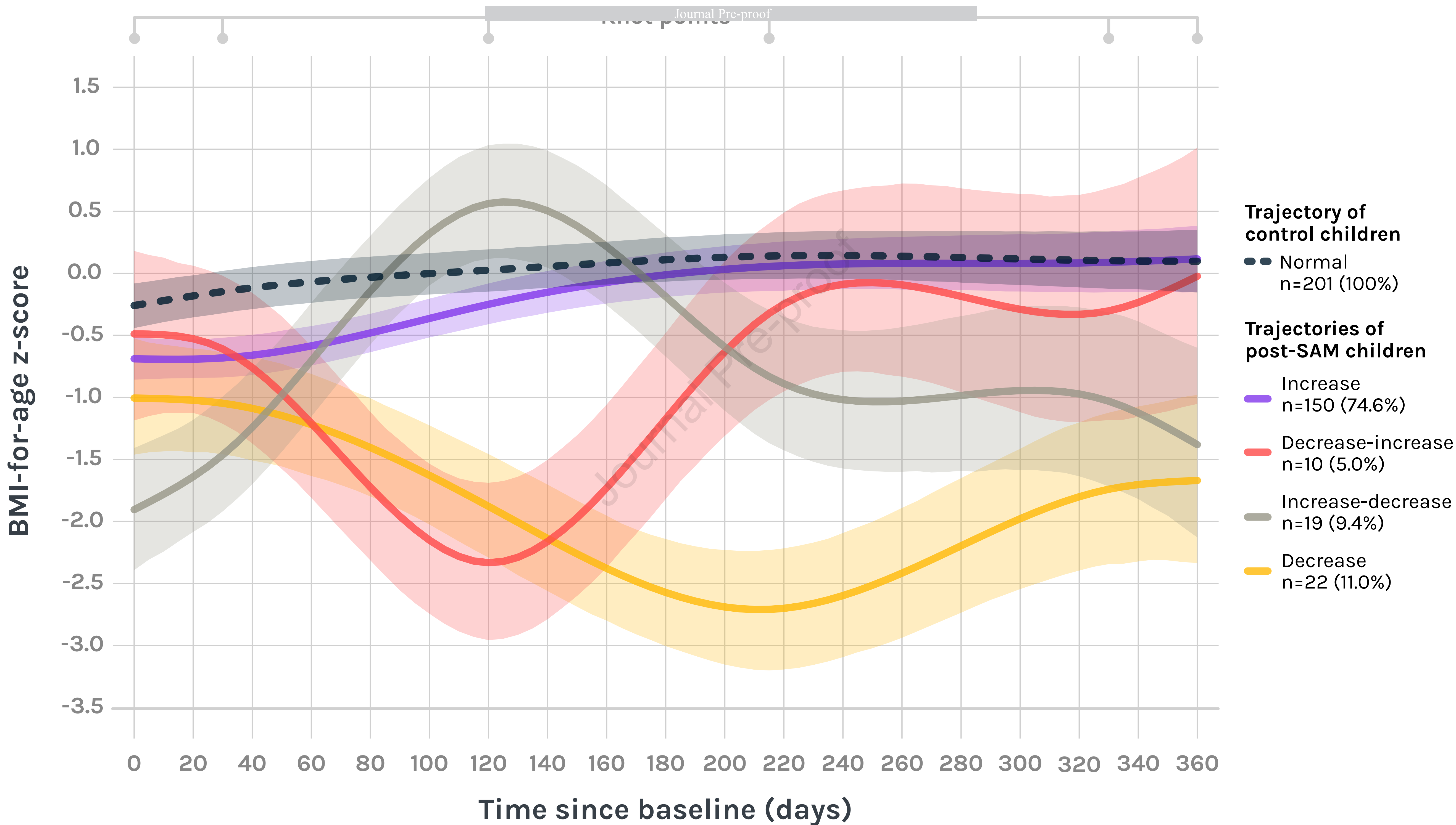
Figure 2: Distinct BMI-for-age z-score (BAZ) trajectories of children in the first-year post-recovery from severe acute malnutrition (solid lines) and controls (dashed line), derived from the latent class trajectory modeling. The shaded areas indicate the estimated 95% confidence interval.

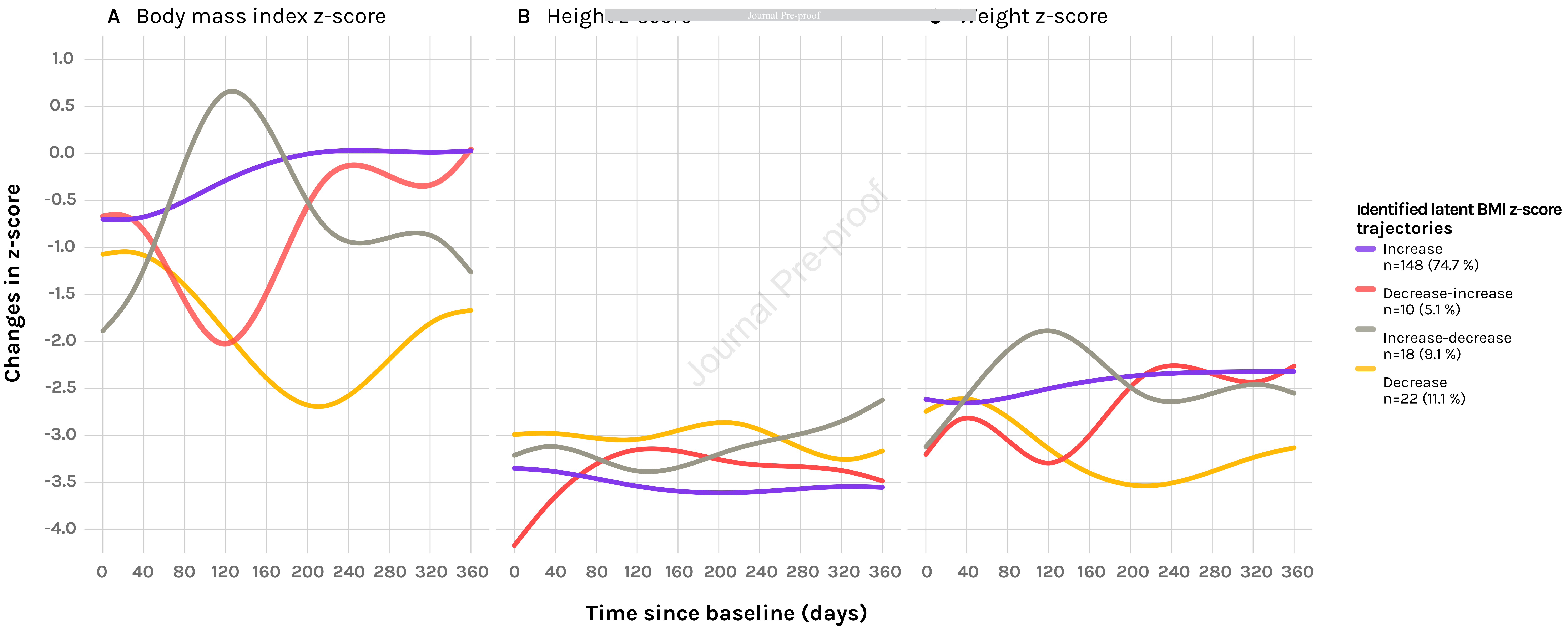
Figure 3: Distinct BMI-for-age z-score trajectories derived from the latent class trajectory modelling with corresponding weight-for-age z-score and height-for-age z-score trajectories.

Figure 4: The coefficients (95% confidence interval) shown on the forest plots are derived from separate multiple linear regression analyses and represent the mean difference in anthropometry and body composition indices between the control group (the reference trajectory) and the 4 distinct BMI-for-age z-score (BAZ) trajectories derived from latent class trajectory analysis among children recovered from SAM group. Model 1 was unadjusted. Model 2 was adjusted for child's sex, childbirth order (firstborn, second born, or ≥ third born) and age (year) at the 5-year post-recovery follow-up. Model 3 was additionally adjusted for season (lean or harvest), food security (no, mild, moderate, or severe food insecurity) and economic status at the time of enrollment (poorest, poorer, middle, or richer).

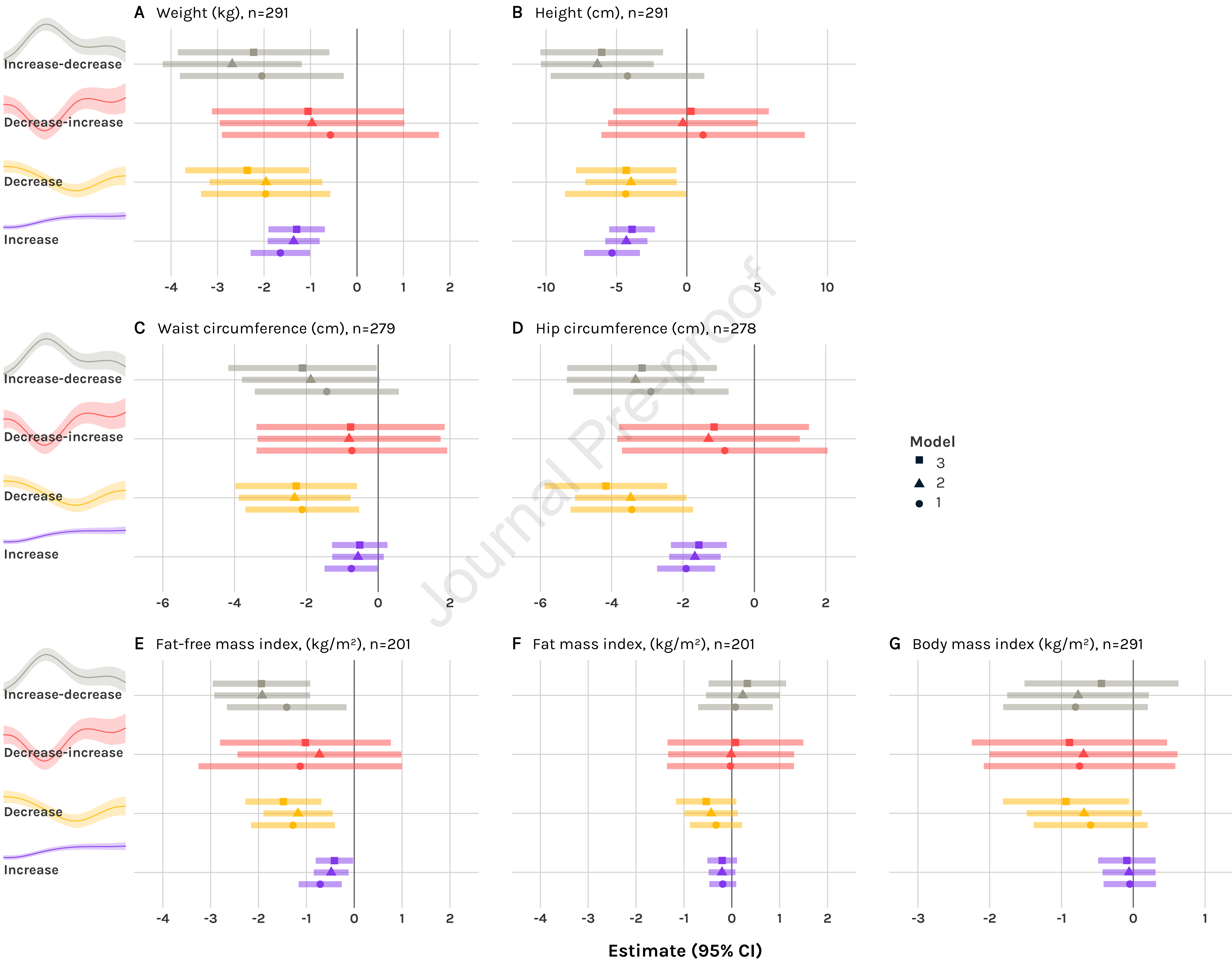
Figure 5: The coefficients (95% confidence interval) shown on the forest plots are derived from separate multiple linear regression analyses and represent the mean difference in concentrations of cardiometabolic markers and blood pressure between the control group (the reference trajectory) and the 4 distinct BMI-for-age z-score (BAZ) trajectories derived from latent class trajectory analysis among children recovered from SAM group. Variables found not to follow a normal distribution (i.e., insulin, triglyceride, HOMA-IR, and blood pressure) were log-transformed prior to the regression analyses. The presented estimates for these variables were backtransformed and shown as percentwise change. Model 1 was unadjusted. Model 2 was adjusted for child's sex, childbirth order (firstborn, second born, or ≥ third born) and child's age (year) at the 5-years follow-up. Model 3 was additionally adjusted for season at discharge (lean or harvest), household food security (no, mild, moderate, or severe food insecurity) and economic status at the time of enrollment to our study (poorest, poorer, middle, or richer). Model 4 was additionally adjusted for fat mass (kg) and height (cm) at the 5-year follow-up.

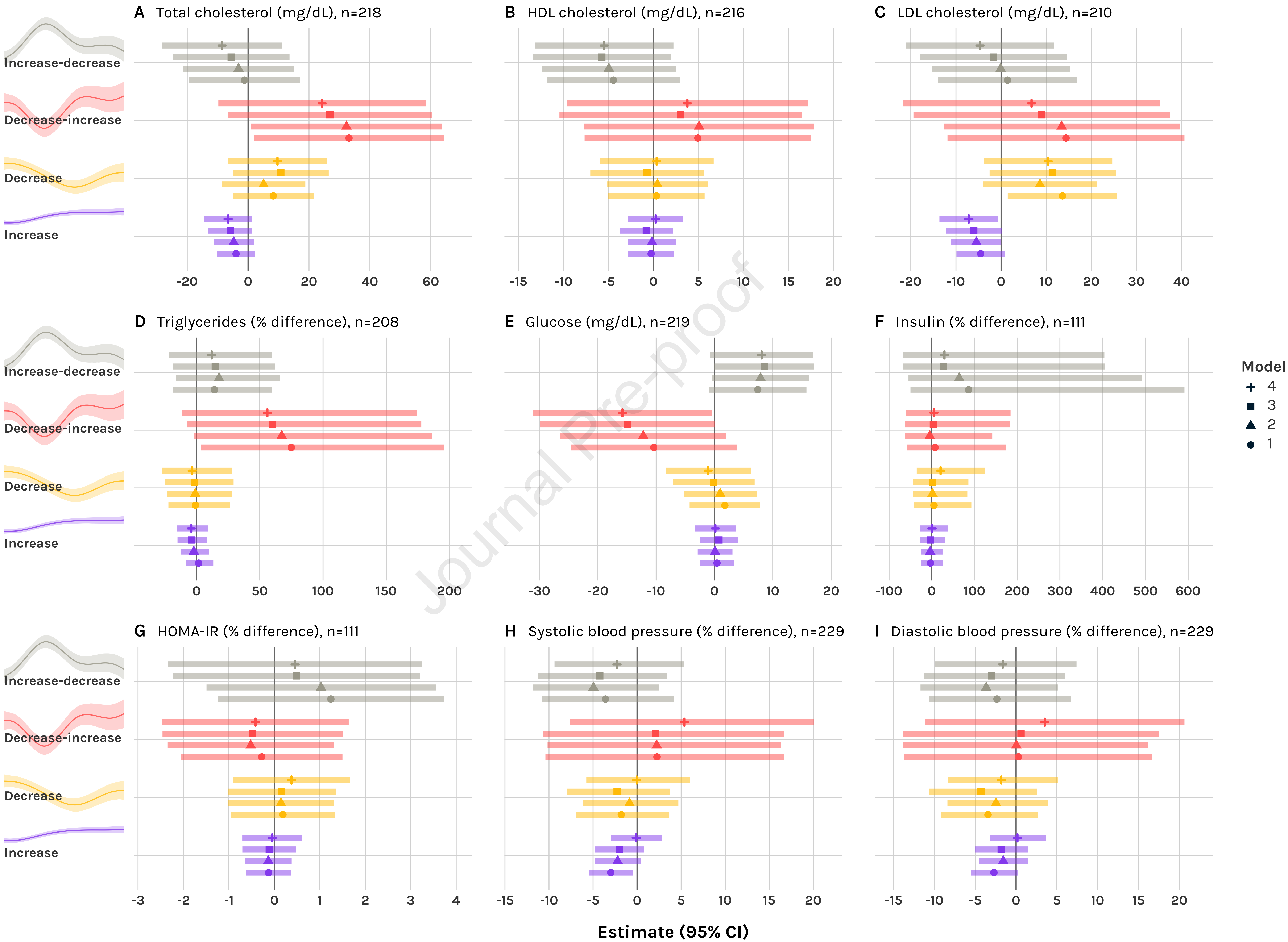

A Total cholesterol (mg/dL), n=218
B HDL cholesterol (mg/dL), n=216
C LDL cholesterol (mg/dL), n=210
D Triglycerides (% difference), n=208
E Glucose (mg/dL), n=219
F Insulin (% difference), n=111
G HOMA-IR (% difference), n=111
H Systolic blood pressure (% difference), n=229
I Diastolic blood pressure (% difference), n=229
Post-SAM children
Post-SAM children
Post-SAM children
Model
4
3
2
1
-15
-10
-5
0
5
-15
-10
-5
0
5
-15
-10
-5
0
5
-15
-10
-5
0
5
10
15
-6
-4
-2
0
2
4
6
-60
-40
-20
0
20
40
60
-60
-40
-20
0
20
40
60
-10
-5
0
5
-10
-5
0
5
Estimate (95% CI)


BMI-for-age z-score
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
Time since baseline (days)
Trajectory of control children
Normal n=201 (100%)
Trajectories of post-SAM children
Increase n=150 (74.6%)
Decrease-increase n=10 (5.0%)
Increase-decrease n=19 (9.4%)
Decrease n=22 (11.0%)



A Body mass index z-score
B Heigh
eight z-score
Changes in z-score
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
0 40 80 120 160 200 240 280 320 360
Time since baseline (days)
Identified latent BMI z-score trajectories
Increase
n=148 (74.7 %)
Decrease-increase
n=10 (5.1 %)
Increase-decrease
n=18 (9.1 %)
Decrease
n=22 (11.1 %)


A Weight (kg), n=291
B Height (cm), n=291
C Waist circumference (cm), n=279
D Hip circumference (cm), n=278
E Fat-free mass index, (kg/m²), n=201
F Fat mass index, (kg/m²), n=201
G Body mass index (kg/m²), n=291
Increase-decrease
Decrease-increase
Decrease
Increase
Model
3
2
1
Estimate (95% CI)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E Glucose (mg/dL), n=219
F Insulin (% difference), n=111
G HOMA-IR (% difference), n=111
H Systolic blood pressure (% difference), n=229
I Diastolic blood pressure (% difference), n=229
Increase-decrease
Decrease-increase
Decrease
Increase
Model
4
3
2
1
Estimate (95% CI)

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tsinuel Girma reports financial support was provided by Office of U.S. Foreign Disaster Assistance (OFDA). Tsinuel Girma reports financial support was provided by United States Agency for International Development (USAID). Tsinuel Girma reports financial support was provided by International Atomic Energy Agency (IAEA). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.