Growth and metabolism in children with acute illness and malnutrition

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Chapter 5

Metabolomic changes in serum of children with different clinical diagnoses of malnutrition

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ABSTRACT

Background: Mortality in children with severe acute malnutrition (SAM) remains high despite standardized rehabilitation protocols. Two forms of SAM are classically distinguished: kwashiorkor and marasmus. Children with kwashiorkor have nutritional edema and metabolic disturbances, including hypoalbuminemia and hepatic steatosis, whereas marasmus is characterized by severe wasting. The metabolic changes underlying these phenotypes have been poorly characterized and whether homeostasis is achieved during hospital stay is unclear. We aimed to characterize metabolic differences between marasmus and kwashiorkor at hospital admission and after clinical stabilization and compare them to stunted and non-stunted community controls.

Methods: We studied children from Malawi, aged 9 to 59 months hospitalized with SAM (n=40; 21 kwashiorkor, 19 marasmus) or living in the community (n=157, 78 stunted, 79 non-stunted) (ISRCTN 13916953). Serum from patients with SAM was obtained at hospital admission and 3 days after nutritional stabilization and from community controls. Using targeted metabolomics, 141 metabolites including amino acids, biogenic amines, acylcarnitines, sphingomyelins, and phosphatidylcholines were measured.

Results: At admission, most metabolites (128 out of 141, 91%) were lower in children with kwashiorkor compared to marasmus, with significant changes in several amino acids and biogenic amines, including those of the kynurenine-tryptophan pathway. Several phosphatidylcholines and some acylcarnitines also differed. SAM patients had profoundly different metabolite profiles compared to stunted and non-stunted controls, even after clinical stabilization. Amino acids and biogenic amines generally improved with nutritional rehabilitation but most sphingomyelins and phosphatidylcholines did not.

Discussion and Conclusions: Children with kwashiorkor were metabolically distinct from those with marasmus and may present more severe metabolic disruptions. Children with SAM showed profoundly different metabolic profiles compared to stunted and non-stunted controls, and this even after clinical stabilization. Therefore, metabolic recovery in children with SAM likely extends beyond discharge, which may explain the poor long-term outcomes in these children.

INTRODUCTION

Severe malnutrition remains a significant global health problem. Each year, it affects over 18 million children, most living in low-income settings and contributes to approximately 45% of all deaths in children under the age of five worldwide.[1] Children that have both severe malnutrition and critical illness are classified as complicated severe malnutrition (cSM) and these children are at high risk of mortality. Even in nutritional rehabilitation centers that follow WHO-established treatment protocols, in-hospital mortality remains high, ranging from 10 to 30% of all treated cases.[2] Post-discharge mortality is also significant, with studies reporting mortality rates of 8.7% within 3 months of discharge;[3] or up to 18% of all treated cases dying within a year of discharge.[4] Furthermore, even if the children survive, they suffer from long-term adverse effects showing patterns of thrifty growth and functional deficits such as weak hand grip and impaired cardiovascular resistance.[5] Children with severe malnutrition also show impaired cognitive function and significant attention deficits.[6,7]

Two clinical phenotypes are classically recognized: severe wasting (SW) and nutritional edema (NE). NE presents with a range of clinical signs including bilateral pitting edema, loss of hair pigmentation, skin lesions, hypoalbuminemia and hepatic steatosis.[8] Historically, NE was associated with higher mortality but case fatalities have shifted toward SW.[9] This change in mortality rates has been attributed to an increased prevalence of co-morbidities including HIV and pneumonia in patients with SW.[10]

The pathophysiological mechanisms underlying the development of SM and its major clinical phenotypes are poorly understood and current literature examining the metabolic changes in cSM is limited. However, some studies have shown that cSM is associated with altered protein, glucose and lipid metabolism.[11,12,13,14] To date, the only comprehensive metabolomics analysis of children with cSM was conducted by Bartz and colleagues in 2014.[15] They showed that it induced significant changes in acylcarnitines, inflammatory cytokines, fatty acids, amino acids, and hormones related to appetite and energy metabolism. However, they lacked a control group and the number of metabolites analyzed was limited.

Metabolic dysregulations such as hypoglycemia, impaired gluconeogenesis, or disrupted amino acid or lipid metabolism could underlie the different clinical manifestations of cSM and explain the differences in mortality. Our objective was to better understand the metabolic disturbances associated with malnutrition. Therefore, we used large-scale targeted metabolomics to examine the metabolite profiles in serum of children with either NE or SW and compared them to community participants (CP).

METHODS

Study population

This observational study examined 40 children aged 9 to 59 months either undergoing in-patient treatment for cSM (NE, 21; SW, 19) at the Queen Elizabeth Central Hospital in Blantyre or living in rural communities (n=157) in southern Malawi.

Complicated severe malnutrition: Children with cSM were recruited from the Nutritional Rehabilitation Unit at the Queen Elizabeth Central Hospital in Blantyre, the largest hospital in Malawi. All children admitted to this unit had medical complications or "danger signs" as defined by the current WHO guidelines,[2] including anorexia, vomiting, convulsions and loss of consciousness. Children were diagnosed with NE if they showed moderate or severe nutritional bilateral pitting edema and other phenotypic changes like hair and skin abnormalities. Edema was graded as: mild (+) when only in the feet; moderate (++) when in the feet, legs and lower arms; and severe (+++) when visible on the upper arm and/or face. SW was defined as a weight-for-height Z-score calculated from WHO growth standards more than 3 SDs below the median and/or if their mid-upper arm circumference (MUAC) was less than 115 mm. Five children showed a mixed SW-NE phenotype having both edema and a MUAC less than 115 mm. For analysis, these children were included in the NE group since results did not differ when excluded.

Recorded clinical data included: anthropometry, appetite, HIV reactivity (or exposure in children <18 months), time-to-nutritional stabilization, and duration of hospital stay. All children with cSM participated in the "TranSAM" clinical trial, which evaluated 3 common re-feeding diets (i.e., F100, ready-to-use food (RUTF) or RUTF/F100). These diets are isocaloric but vary in their composition of carbohydrates and fat ratios. The diets were used during the rehabilitation (post-stabilization) phase of treatment. Children with cSM were block randomized based on HIV status and excluded if they died before nutritional stabilization, were diagnosed as NE but had only mild edema, had confirmed or suspected malaria and/or tuberculosis, or had insufficient serum for analysis. Informed consent was obtained from legal guardians and the study was approved by the University of Malawi College of Medicine Research and Ethics Committee, and by the Hospital for Sick Children in Toronto, Canada. The clinical study was registered (ISRCTN 13916953).

Community participants: The CP (n=157) were recruited from six villages in Malawi as previously describe.[16] Children were from families who primarily relied on subsistence farming which is highly vulnerable to climatic disruptions. The typical diet among these children is mainly composed of cereals (i.e., maize) and starchy fruits (plantain) and roots (cassava and potatoes) and is low in protein, especially from animal sources. Enrolled children were weighed and measured by

experienced field workers; stunted children were identified as having a height-for-age z-score of 2 SD below the median as calculated from WHO growth standards. Children were enrolled if they did not have SM, congenital or chronic disease, or recent diarrhea. CP were age- and sex-matched with cSM cohort using an automated function implemented in the R package MatchIt.[17] HIV status was not tested in CP but these children were asymptomatic and thought to be negative. For community recruited children, informed consent was obtained from legal guardians and the study was approved by the University of Malawi College of Medicine Research and Ethics Committee, by the Human Research Protection Office of Washington University in St. Louis, and by the John Hopkins School of Medicine Institutional Review Board.

Serum collection and metabolite measurements

For cSM patients, blood samples were collected at admission within 24 hours of enrolment and three days after clinical stabilization as defined by WHO criteria.[18] Clinically stable children were transitioned from a standard F-75 diet to the F-100 and/or RUTF, thus the point of clinical stabilization coincides with diet transition. Children were not fasted prior to blood collection, but at admission children with cSM can suffer from anorexia and may be in a fasted state. After collection, blood was spun and the serum obtained was stored at -80°C until further analysis. For metabolomics, samples were analyzed using liquid chromatography tandem mass spectrometry and the Absolute*IDQ*™ p180 Kit (Biocrates Life Sciences AG, Innsbruck, Austria). This analytical method conforms with the FDA Guideline 'Guidance for Industry—Bioanalytical Method Validation (May 2001)', and is reproducible and comparable across analytical sites.[19] **Supplemental Tables 1-8** lists all metabolites (n=188) and other markers (n=5, Supplemental Table 8) that were originally targeted**.** These include the following compound classes: sugars (i.e. the sum of all hexoses including glucose, Supplemental Table 8), amino acids (n=21, Supplemental Table 1), biogenic amines (n=21, Supplemental Table 2), sphingomyelins (n=15, Supplemental Table 3), acylcarnitines (n=40, Supplemental Table 4) and phosphatidylcholines (n=90); which include lysophosphatidylcholine (n=14, Supplemental Table 5), phosphatidylcholine acyl-alkyls (n=38, Supplemental Table 6), and phosphatidylcholine diacyl (n=38, Supplemental Table 7). In total, 141 metabolites passed quality control cut-offs (i.e. had a mean coefficient of variation < 25% across different experimental batches, had less than 10% missing values, and had a median value greater than or equal to the lower limit of quantification in at least one study group). Additional markers including albumin and electrolytes (i.e., potassium, sodium, phosphate and magnesium, Supplemental Table 8) were measured by routine clinical laboratory platforms in patients with cSM but not in CP.

Statistical analysis

To assess differences in metabolite profiles, we conducted both univariate and Partial Least Squares (PLS) multivariate analyses. Sample outliers were assessed by principal component analysis and

removed (n=1; SW at admission; n=1, stunted CP). Concentrations below the lower limit of detection were set at 0 and missing values were imputed using bagimpute implemented in the R package caret.[20] Values were offset by 1, log transformed, mean centered and scaled. Partial Least-Square discriminative analysis (PLS-DA) was conducted on age and sex corrected values with the mixOmics package.[21] Multilevel PLS-DA was performed between admission and nutritional stabilization to account for repeated measures. The predictive power of the PLS components to discriminate between groups was assessed by classification error rates based on the maximum distance obtained from 10-fold cross-validation. This was run iteratively 10 times and the mean classification error rate for left out cases was calculated. Sparse PLS-DA (sPLS-DA) was used to select the 10 features that best distinguish patients with NE or SW at admission. This method can identify the most robust and stable discriminating variables, i.e., those selected in the top-10 discriminative features more than 80% of the time upon cross-validation and had a Variable Importance in Projection (VIP) score greater or equal to 1. VIP is an estimate of the importance of each variable in the projection of the PLS-DA model and used for variable selection. Mixed effects models were developed on log-transformed and scaled variables to assess differences in children with or without edema at admission and after clinical stabilization while accounting for age, sex and repeated measures (i.e., patient IDs were included as random factors). Linear regression models were used to compare samples that did not include repeated measures (i.e., when not comparing admission to after clinical stabilization). To control for multiple testing, p-values were adjusted using False Discovery Rate (FDR). Dendrograms reflecting Pearson based hierarchal clustering of all metabolite concentrations obtained from cSM patients at admission and nutritional stabilization were created to order the presented standardized estimates and SEMs obtained from group comparison. Scaled estimates and SEMs allows the comparison of effect sizes across different metabolites. R software (version 3.2.3) was used for all analysis and figures were generated with the ggplot2 package and Inkscape.

RESULTS

The characteristics of the children with cSM who had either SW or NE as well as those of the stunted or non-stunted CP are presented in **Table 1**. SW children tended to be younger than the other groups. cSM patients with NE or SW had a similar time to stabilization, and length of hospital stay.

Table 1. Characteristics of patients hospitalized with complicated severe malnutrition, including severe wasting and nutritional edema, and of stunted and non-stunted community participants.

	cSM			CP		
	All	NE[2]	SW	All	Stunted	Non-Stunted
	n=39	n=21	n=19	n=157	n=78	n=79
Female, n(%)	21 (54%)	12 (57%)	10 (53%)	91 (58%)	45 (58%)	46 (58%)
HIV reactive, n(%)	19 (49%)	9 (43%)	10 (53%)	–	–	–
Age, months	26.8 ±13.0	30.8 ±13.6	21.4 ±10.9	29.4 ±11.8	30.9 ±11	27.8 ±12.5
Length, cm	76.7 ±8.9	80.8 ±7.7	71.4 ±7.7	83.3 ±7.9	81.2 ±6.4	85.4 ±8.7
Height-for-age, Z-score	-3.5 ±1.9	-2.9 ±1.9	-4.1 ±1.7	-2.0 ±1.3	-3 ±0.9	-1.0 ±0.9
Weigth-for-age, Z-score	-3.9 ±1.8	-2.8 ±1.5	-5.1 ±1.0	-1.0 ±1.0	-1.5 ±1.0	-0.45 ±0.8
Weight-for-height, Z-score	-2.9 ±1.9	-1.7 ±1.6	-4.4 ±0.9	0.2 ±0.9	0.25 ±1.0	-0.14 ±0.7
MUAC, cm	11.6 ±1.8	12.7 ±1.6	10.2 ±1.0	–	–	–
Time to stabilization[ŧ], days	3 (2 – 4)	3 (2 – 4)	3 (2 – 4.5)	–	–	–
Duration of stay, days	9 (9 – 14)	9 (9 – 14)	9 (8 – 14)	–	–	–

Data are presented as n (%), means ± SDs, or median (IQR). [2]Patients with nutritional edema (NE) had either moderate or severe edema. [ŧ]Stabilization coincides with diet transition (i.e. when children are transitioned from F75 diet to F100 and/or RUTF). CP, community participants; MUAC, mid-upper arm circumference; cSM, complicated severe malnutrition; SW severe wasting.

Children with different forms of complicated severe malnutrition are metabolically distinct from community participants.

Metabolic profiles differed between children with NE compared to SW at admission, and both cSM phenotypes were profoundly different metabolically from CP. Mean concentration and SDs of all 141 metabolites measured with targeted liquid chromatography tandem mass spectrometry are presented stratified by group; and differences in metabolites between groups are detailed in **Supplemental Tables 9-26**. These include amino acids (Supplemental Tables 9-10), biogenic amines (Supplemental Tables 11-12), sphingomyelins (Supplemental Tables 13-14), acylcarnitines (Supplemental Tables 15-16), lysophosphatidylcholines (Supplemental Tables 17-18), phosphatidylcholine acyl alkyls (Supplemental Tables 19-20), phosphatidylcholine diacyls (Supplemental Tables 21-22), other markers (Supplemental Tables 23-24) and summary values and metabolite ratios (Supplemental Tables 25-26).

PLS-DA was used to distinguish children with NE versus those with SW using metabolites measured in serum obtained at hospital admission (**Figure 1A**). Although children with NE or SW formed distinct clusters, the classification error rate based on maximum distance was still 30%. After nutritional stabilization, these children were indistinguishable based on their circulating metabolites as the mean classification error rate was 44 %, which is not significantly better than chance (**Supplemental Figure 1**). Therefore, after nutritional stabilization children with NE and SW have similar metabolic profiles. We then compared groups of children with either NE or SW at admission to stunted CP. As expected, these children were profoundly different metabolically from stunted children (**Figure 1B**). To assess metabolic recovery in children with cSM, we compared their metabolic profiles at admission to after nutritional stabilization (**Figure 1C**). Samples obtained before and after nutritional stabilization could be readily distinguished using PLS-DA with an average classification error rate of 6.9%. Finally, we found that cSM patients showed significantly different metabolic profiles from those of CP and this both at admission and after clinical stabilization (**Figure 1D**). Thus, metabolic disturbances linger in children with cSM even after achieving nutritional stabilization.

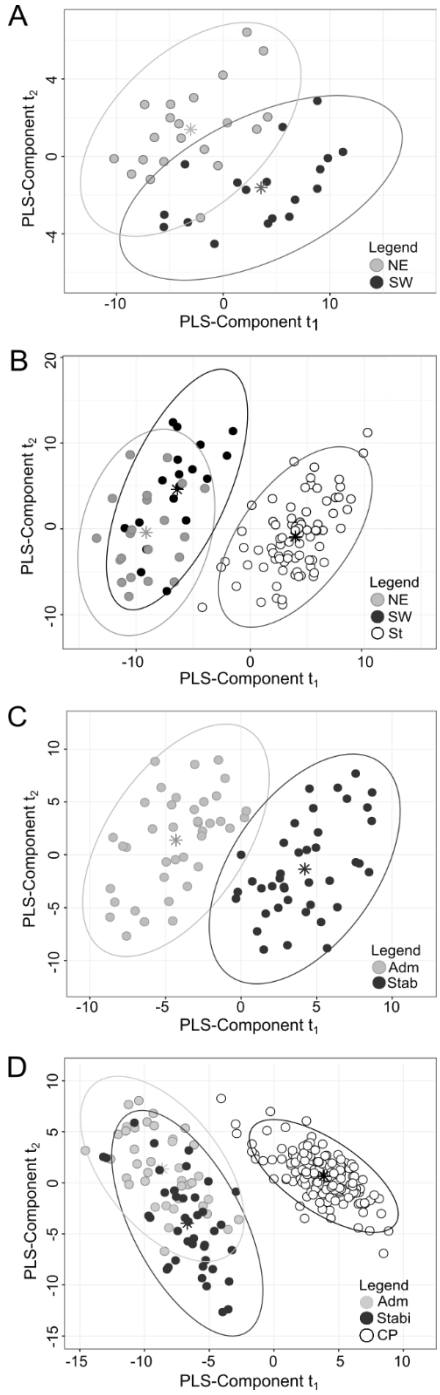

Figure 1. PLS-DA t_1 versus t_2 score plots derived from the analysis to distinguish **A)** children with NE versus SW at admission; **B)** children with NE or SW at admission versus stunted CP; **C)** cSM patients at admission versus after clinical stabilization; **D)** cSM patients at admission and after nutritional stabilization versus CP (including both stunted and non-stunted children). PLS-DA analysis was performed on age- and sex-adjusted concentrations of metabolites and additional markers. These were measured in serum of children with cSM at hospital admission and after nutritional stabilization or in serum of stunted and non-stunted CP. Multilevel PLS-DA analysis was used to compare children at admission versus discharge which accounts for repeated measures within patients. Adm, admission; CP, community participant; NE, nutritional edema; Stab, stabilization; Stt, stunted; SW, severe wasting.

Specific metabolite differences between children with complicated severe malnutrition and community participants

We then evaluated the specific metabolites that differed between: 1) children with either NE or SW; 2) children with cSM at admission and after nutritional stabilization; and 3) children with cSM after stabilization and CP (**Figures 2** and **3** and **Supplemental Tables 9-26**).

When children with NE were compared to those with SW, we found that at admission most metabolites (128/141, 91%) were lower in NE; although only 31 of these achieved statistical significance (**Figure 2A** and **3A**). Almost all amino acids were lower in NE at admission and essential amino acids were significantly more depleted (mean ± SD; 405 ±133 μmol/L in NE vs 521 ±148 μmol/L in SW, FDR-adjusted $p < .02$). Specific differences were found in lysine (97 ± 26 μmol/L in NE vs 132 μmol/L ± 48 in SW, FDR-adjusted $p < .03$), threonine (36 μmol/L ± 16 in NE vs 70 μmol/L ± 34 in SW, FDR-adjusted $p < .0004$), methionine (10.7 μmol/L ± 3.6 in NE vs 15.2 μmol/L ± 5.1 in SW, FDR-adjusted $p < .03$), aspartic acid (15.6 μmol/L ± 10.2 in NE vs 25.6 μmol/L ±14.1 in SW, FDR-adjusted $p < .009$) and tryptophan (4.9 μmol/L ± 3.7 in NE vs 12.4 μmol/L ±11.0 in SW, FDR-adjusted $p < .003$) along with its derivative the biogenic amine kynurenine (0.91 μmol/L ± 0.81 in NE vs 2.21 μmol/L ± 1.58 in SW, FDR-adjusted $p = .004$) (Figure 2A). However, the kynurenine-to-tryptophan ratio did not differ, as both metabolites were proportionally lower in NE. Also, serotonin was not different between groups, nor was the serotonin-to-tryptophan ratio (Supplemental Tables 25-26). Electrolyte concentrations were similar between groups. However, those with NE did have lower circulating albumin (Figure 2A and Supplemental Tables 23-24).

Apart from these differences in amino acids and biogenic amines, many other metabolites were significantly lower in NE. These included: 7 phosphatidylcholine acyl-alkyls (PC ae C40:6, PC ae 38:6, PC ae C38:4, PC ae C38:0, PC ae C36:4, PC ae C36:2, PC ae C30:0) and 15 phosphatidylcholine diacyls (PC aa C38:3, PC aa C36:3, PC aa C34:4, PC aa C36:5, PC aa C28:1, PC aa C30:0, PC aa C36:6, PC aa C38:5, PC aa C36:4, PC aa C38:4, PC aa C40:4, PC aa C40:6, PC aa C38:6, PC aa C34:1, PC aa C34:2) and two acylcarnitines (C14:1 and C18:1) (**Figures 2A** and **3A** and Supplemental Tables 15-16 and 19-22). The acetylcarnitine-to-free carnitine ratio (C2/C0) can be used as a measure of beta-oxidation of even-numbered fatty acids and was found to be lower in NE patients (mean ±SD; 0.61 ± 0.57 in SW vs 0.27 ± 0.18 in NE, Supplemental Tables 23-24.

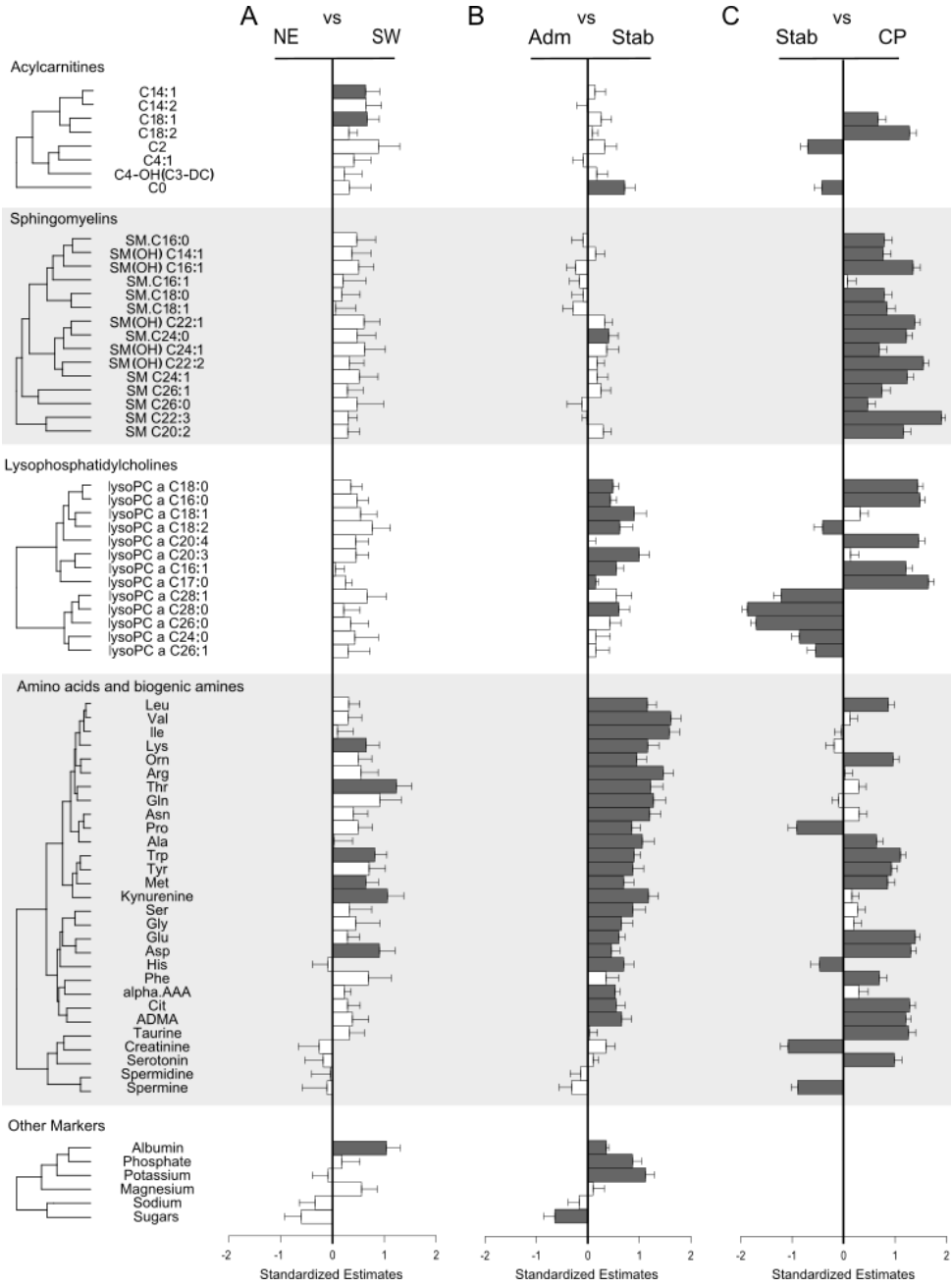

Figure 2. Serum metabolites of acylcarnitines, sphingomyelins, lysophosphatidylcholines, amino acids and biogenic amines as well as other markers were compared between **A)** children with NE versus SW; **B)** children with cSM at admission versus after clinical stabilization and **C)** after nutritional stabilization and CP (including both stunted and non-stunted children). Standardized estimates and SEMs were obtained from either mixed linear regression models that accounted for age, sex and repeated measures (i.e., when

comparing admission and after nutritional stabilization) or linear regression models adjusted for age and sex. Metabolites are ordered based on Pearson hierarchal clustering of all metabolites within each compound class from cSM patients at admission and after nutritional stabilization and clustering is represented by the dendrograms. Scaled estimates and SEMs allowed the comparison of effect sizes across different metabolites. The direction of the bar indicates which diagnostic group had higher metabolite levels, and the metabolites that reached FDR-adjusted significance are labelled in dark grey. All metabolite abbreviations are detailed in Supplemental Tables 1-8. Adm, admission; CP, community participant; cSM, complicated severe malnutrition; NE, nutritional edema; SW, severe wasting; Stab, stabilization.

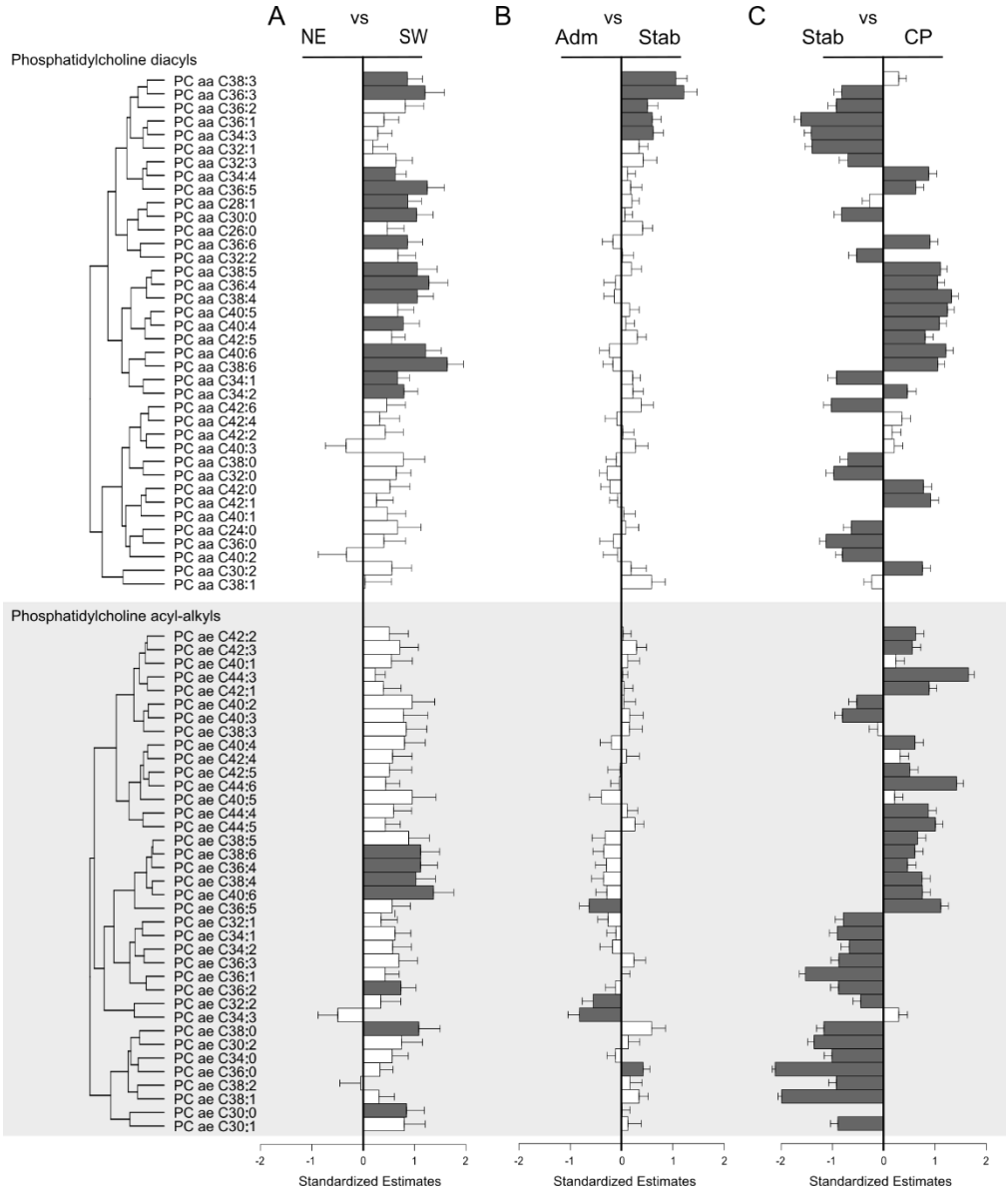

Figure 3. Serum metabolites of phosphatidylcholine diacyls and acyl-alkyls were compared between **A)** children with NE versus SW; **B)** children with cSM at admission versus after clinical stabilization and **C)** after nutritional stabilization and CP (including both stunted and non-stunted children). Standardized estimates and standard errors were obtained from either mixed linear regression models that accounted for age, sex and repeated measures (i.e., when comparing admission and after nutritional stabilization) or linear regression models adjusted for age and sex. Metabolites are ordered based on Pearson hierarchal clustering of all metabolites within each compound class from cSM patients at admission and after nutritional stabilization and this clustering is represented by the dendrograms. Scaled estimates and SEMs allowed the comparison of effect sizes across different metabolites. The direction of the bar indicates which diagnostic group had higher metabolite levels, and the metabolites that reached FDR-

adjusted significance are labelled in dark grey. All metabolite abbreviations are detailed in **Supplemental Tables 1-8**. Adm, admission; CP, community participant; cSM, complicated severe malnutrition; NE, nutritional edema; SW, severe wasting; Stab, stabilization.

Finally, we used sparse PLS-DA to select the top discriminating metabolites that best distinguish between NE and SW at admission. Using 10-fold cross-validation, nine metabolites were robustly and stably (>80%) selected as being in the top-10 distinguishing features. The metabolites were: tryptophan, kynurenine, threonine, PC aa C36:4, PC aa C38:6, PC aa C40:6, PC aa C34:1, PC aa C34:2, and albumin (**Figure 4** and **Supplemental Table 27**). These metabolites were specifically lower in patients with NE, whereas patients with SW had either intermediate or similar levels to CP.

Metabolite differences in children with complicated severe malnutrition at admission compared to after nutritional stabilization

Two main clusters of correlated metabolites increased with nutritional stabilization (**Figures 2B** and **3B**). The first cluster (n= 23) was mainly composed of amino acids (leucine, valine, isoleucine, lysine, ornithine, arginine, threonine, glutamine, asparagine, proline, alanine, tryptophan, tyrosine, methionine, serine, glycine, glutamic acid, aspartic acid, histidine, citrulline) and the biogenic amines kynurenine, alpha AAA and ADMA. The sum of all amino acids, including that of essential amino acids, was increased in cSM patients after stabilization (mean ± SD; 2000 ±740 µmol/L at admission vs 3190 ± 1160 µmol/L after stabilization, FDR adjusted $p < .0001$) (**Supplemental Figure 2** and **Supplemental Table 25-26**). This increase in circulating amino acids and biogenic amines could suggest the restoration of proteogenic capacity and nitrogen homeostasis but may also reflect other processes (e.g., this could indicate increased demand for these metabolites). However, the achieved levels of amino acids and biogenic amines were significantly lower than those of CP. The kynurenine-to-tryptophan ratio did not differ between admission and after stabilization, as both metabolites increased proportionally, although this ratio was higher than in CP (**Supplemental Figure 25-26**). The serotonin-to-tryptophan ratio was significantly decreased after stabilization as serotonin was low at admission and stayed low after stabilization. There was also an increase in circulating albumin, phosphate and potassium while the total sum of hexoses (i.e. total sugars) decreased after nutritional stabilization (**Figure 2B**). Furthermore, several phosphatidylcholines were significantly higher in cSM patients after nutritional stabilization (**Figure 3B**). These included lysophosphatidylcholines (lysoPC a C18:0, lysoPC a C16:0, lysoPC a C18:1, lysoPC a C18:2, lysoPC a C20:3, lysoPC a C16:1, lysoPC a C17:0, lysoPC a C28:0) and phosphatidylcholine diacyls (PC aa C38:3, PC aa C36:3, PC aa C36:2, PC aa C36:1, PC aa C34:3). Of the acylcarnitines and sphingomyelins, only C0 and SM C24:0 were significantly higher.

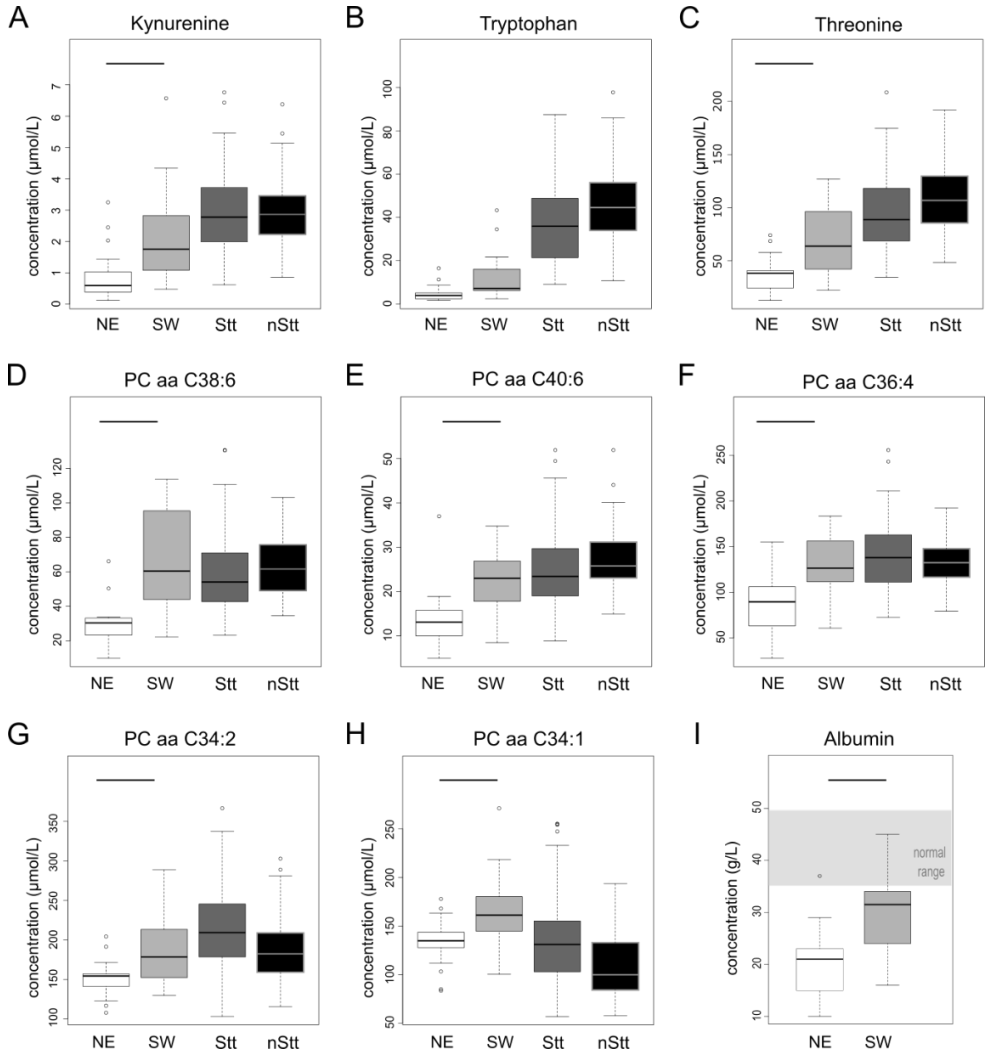

Figure 4. Concentrations of serum metabolites that most robustly discriminate between children with NE and SW at admission as identified by sparse PLS-DA. These include the biogenic amines and amino acids A) kynurenine, B) tryptophan and C) threonine, with 5 phosphatidylcholine diacyls D) PC aa C38:6, E) PC aa C40:6, F) PC aa C36:4, G) PC aa C34:2, H) PC aa C34:1 and I) albumin. Boxplots summarize the median (midline) and interquartile range (upper and lower box). Groups are as follows: NE, n=21; SW, n=18; stunted CP, n=78; and non-stunted CP, n=79. Cross-line at top indicates significant differences between NE and SW at admission as obtained by both PLS-DA (VIP score ≥ 1 and feature stability ≥ 80%) and linear regression models (FDR-adjusted p-values < 0.05). Albumin was not measured in CP; light-grey zone indicates normal clinical range of circulating albumin in children. All metabolite abbreviations are detailed in Supplemental Tables 1-8. CP, community participant; NE, nutritional edema; SW, severe wasting; nStt, non-stunted; Stt, stunted.

However, other metabolites were found to be significantly higher in patients after nutritional stabilization than in CP (**Figures 2A** and **2B**). This included proline, histidine, creatinine, spermine, the acylcarnitines C2 and C0, the lysophosphatidylcholines lysoPC a C18:2, lysoPC a C24:0, lysoPC a C26:0, lysoPC a C26:1, lysoPC a C28:0, and lysoPC a C28:1 and several phosphatidylcholine diacyls (15 out of 38) and acyl-alkyls (16 out of 38).

In fact, 81% of metabolites (i.e., 107 out of the 132 metabolites available in CP) were still significantly different in children with cSM after nutritional stabilization compared to CP (**Figures 2C** and **3C** and Supplemental Table 9-26). These included: amino acids (12 out of 21), biogenic amines (5 out of 7), acylcarnitines (4 out of 4), sphingomyelins (14 out of 15), as well as lysophosphatidylcholine (11 out of 13), phosphatidylcholine diacyls (30 out of 36) and acyl-alkyls (31 out of 37). The large number of metabolites that did not return to levels seen in CP is especially striking. Therefore, children with cSM that have been stabilized are still metabolically very different from CP, and this even when they are compared exclusively to stunted children.

DISCUSSION

Despite cSM being a major contributor to childhood mortality in low-income countries, its etiology and progression of metabolic disturbances are not well understood. Here, we used targeted metabolomics to measure circulating metabolites in the serum of children with cSM treated in a nutritional rehabilitation center. We aimed to 1) identify metabolic signatures that could distinguish patients with NE from those with SW, 2) compare their profiles to those of CP and 3) identify the metabolic pathways that respond to nutritional rehabilitation.

Our analysis suggests that metabolic profiling *can* distinguish between NE and SW, although there is considerable overlap between groups. The availability of amino acids, especially that of essential amino acids, was more reduced in NE and this may relate to differences in metabolic flux of amino acids that was previously demonstrated in NE.[13,22] Also, aspartic acid, tryptophan and its derivative kynurenine were more depleted in NE. However, the kynurenine-to-tryptophan ratio, a surrogate measure of the activity of indoleamine 2,3-dioxygenase (IDO) (i.e., the rate-limiting enzyme in the synthesis of kynurenine from tryptophan), did not change. Tryptophan may be the most limiting essential amino acid, as once it is metabolized into either serotonin or kynurenine it is no longer available for protein synthesis.[23] Also, reductions in tryptophan to kynurenine catabolism due to defective IDO activity have been associated with liver inflammation and hepatic fibrosis[24] as seen in non-alcoholic fatty liver disease. It is tempting to speculate that low kynurenine could be associated to the hepatic steatosis seen in NE. Tryptophan, and kynurenine are also precursors for *de novo* biosynthesis of nicotinamide adenine dinucleotide (NAD) in humans via quinolinic acid[25]

which is itself derived from aspartate. NAD is an important co-enzyme linked to the generation of energy in the TCA cycle. The tryptophan-kynurenine pathway has also been implicated in mood disorders and major depression[26,27] and children with NE are clinically more irritable and apathetic than those with SW.[28] This pathway has also been shown to be modulated by inflammation, HIV and anti-retroviral treatment in an HIV-positive South African population.[29] It would be interesting to study how the kynurenine-tryptophan pathway is modified by HIV infection in NE and SW. Low tryptophan availability may also be related to the depletion of albumin in NE since it normally binds 80-90% of tryptophan in circulation.[23] Finally, children with NE had lower circulating threonine. This amino acid is an important component of mucin-2 that is secreted by goblet cells to maintain the intestinal barrier.[30] The lower threonine in NE may reflect a more severe barrier dysfunction which is known to be severely compromised in children with cSM.[31]

Compared to those with SW, children with NE had lower concentrations of two acylcarnitines and of the C2/C0 acylcarnitine ratio, a marker of beta-oxidation. Others have also reported lower levels of acylcarnitines in children with NE.[32] This may indicate a reduction of fatty acid transport into the mitochondria via the carnitine shuttle, thus limiting beta-oxidation.[33] Interestingly, carnitine biosynthesis is an NAD-dependent process that requires the amino acids – lysine and methionine, [34] which are also more depleted in NE. Taken together these interconnected pathways may provide a link between the depletion of acylcarnitine, lysine, methionine, aspartate, tryptophan, kynurenine, and albumin which were all significantly lower in children with NE compared to SW.

The other main cluster of metabolites that differed between NE and SW were the phosphatidylcholine diacyls PC aa C36:4, PC aa C38:6, PC aa C40:6 which were all lower in NE whereas levels in SW were similar to CP. A piglet model of protein energy malnutrition (created to mimic NE) also had lower phospholipid levels, which modified the composition of the intestinal lipid membrane.[35] Phosphatidylcholines are the main component of the phospholipid layer of plasma membranes. Their depletion in NE could constrain cellular turn-over in tissues such as the skin and the intestinal lining which need constant replenishing.

Several metabolites differed between children with cSM at admission and after nutritional stabilization. Many were increased, especially amino acids, biogenic amines, and some lysophosphatidylcholines. However, most sphingomyelins and phosphatidylcholines did not recover, which may be a reflection of hepatic dysfunction or lipid malabsorption that has been previously associated with cSM.[36] Furthermore, increased gut permeability has been linked to low circulating sphingomyelins and phosphatidylcholines.[37] Considering this, our results suggest that gut barrier function is slow to recover in children with cSM.

Overall, metabolites levels in the cSM cohort remained remarkably different to both stunted and non-stunted CP, even after stabilization. Several metabolites were actually higher in cSM patients than in CP, which probably does not reflect better nutritional status but persistent metabolic dysregulations. Thus, metabolic homeostasis is likely not restored in children with cSM before discharge, even though they appear to be clinically recovered. Many children die after hospital discharge,[10] and persistent metabolic derangements could contribute to post-discharge mortality. Some metabolites may be useful biomarkers to predict recovery or poor outcome in children prior to discharge; this could be addressed by future studies. Also, it is unknown whether metabolic recovery could be accelerated with longer clinical management, and/or specific nutritional supplements (e.g. niacin for NAD production, or eggs which have the highest content of both tryptophan and phosphatidylcholines).

Finally, if the metabolic changes induced by cSM persist this may lead to long-term consequences that extend into adulthood. For example, sphingomyelins, which are essential for neural myelination, do not recover after nutritional stabilization. Their synthesis depends on phosphatidylcholines, which also show a delayed recovery. Therefore, low levels of sphingomyelins may extend well beyond discharge. In fact, stunted children living in rural villages in Malawi have lower levels of circulating sphingomyelin compared to non-stunted children.[16] Considering the important developmental stage of these children, persistently low sphingomyelins could, at least in part, explain the long-term developmental consequences of childhood malnutrition.[38] Also, many low-income countries are increasingly faced with a nutritional "double burden" as those who developed cSM in childhood tend to become obese and develop type II diabetes (T2D) when challenged by an obesogenic environment in adulthood.[39] It is unclear if the metabolic derangements associated with childhood cSM persist into adulthood and induce adverse metabolic responses to obesogenic environments.

There are several limitations in this study, the most important being the difficulty of relating metabolite changes to specific physiological processes. In normal basal conditions, a metabolite change may indicate a certain physiological state but be associated with a different phenomenon in a severely metabolically deranged population such as children with cSM. Also, the number of patients was relatively low, and we did not have specific data on the timing of blood draws in relation to the last meal which adds variability. Given the changes found in amino acid and lipid metabolism, it would have been valuable to measure more metabolites of the kynurenine-tryptophan pathway and of the TCA cycle. Also, having a longer follow-up would have helped to establish the duration of the metabolic changes. Finally, we only investigated cases of complicated cSM, which represent a relatively small proportion of the global burden of severe malnutrition, children with moderate wasting should also be investigated. The metabolic profile of children with only severe malnutrition may be more similar to that of CP.

In conclusion, we used targeted metabolomics to identify metabolic disturbances in children with cSM. We found that most metabolites were lower in those with NE compared to SW. These different clinical phenotypes may relate to specific dysregulations: 1) of amino acid metabolism, especially that of the kynurenine-tryptophan pathway, 2) of acylcarnitines which regulate fatty acids oxidation, and 3) of phosphatidylcholines which are major components of the plasma membranes. Nutritional rehabilitation of children with cSM improved several metabolites mainly amino acids, biogenic amines, and lysophosphatidylcholines. However, most lipid metabolites such as sphingomyelins, phosphatidylcholine diacyls, and acyl-alkyls did not. In fact, even after nutritional stabilization, the metabolic profiles of children with cSM were still very different from those of stunted and non-stunted CP. These results clearly indicate that, although metabolic homeostasis may be on the path towards recovery, severe metabolic derangements still impair the physiological functioning of children that appear to be clinically stabilized, and these may lead to long term consequences.

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Transparency declarations

None to declare.

Author contributions:

Funding: RHJB. Analysis concept and design: VD, CB, RDS, IT, RM, ES, MJM, JP, WV, and RHJB. Study coordination: VD, CB, RDS, IT, MIO, SS, ES, MJM, LZ, WP, and RHJB. Study supervision: RHJB. Data collection: CJV and LZ. Data management: VD, CJV, MIO, and CB. Data cleaning and verification: VD, DXW, CJV and CB. Data analysis: VD, CB and DXW. Data interpretation: VD, DXW, CB, IT, RM, and RHJB. First draft: VD, and CB. Critical review: VD, CB, RDS, IT, RM, MJM, DXW, ES, SS, CJV, WV, IT, RM, MIO, LZ, JP and RHJB. All authors had access to the data and were responsible for decisions regarding publication

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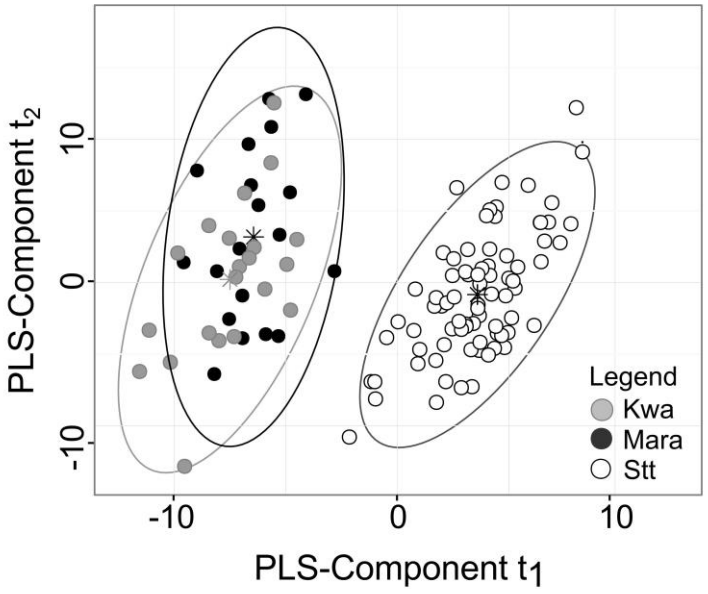
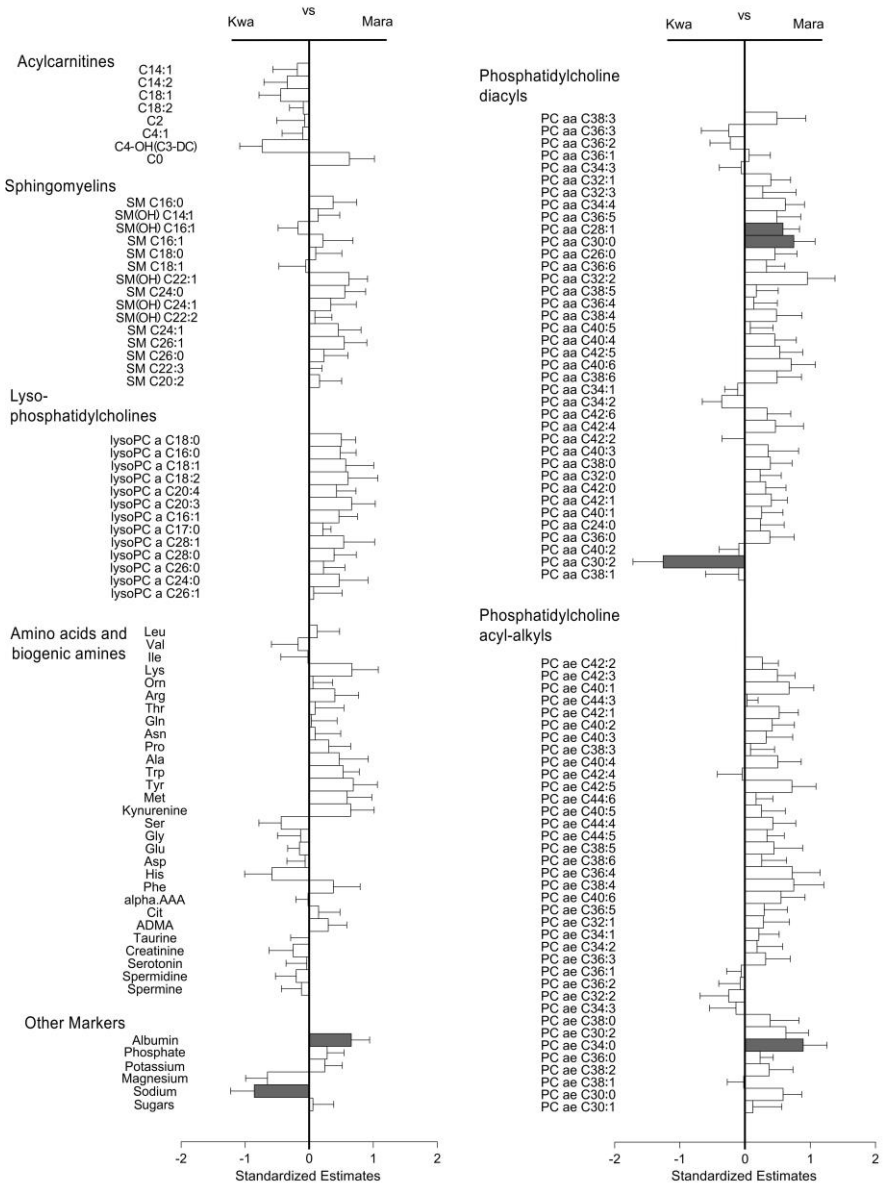
Supplemental materials

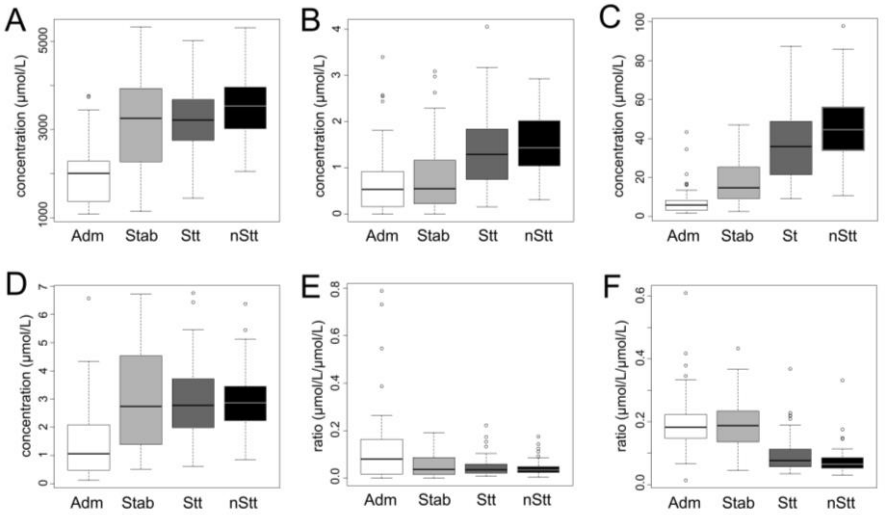
Metabolomic changes in serum of children with different clinical diagnoses of malnutrition



Supplemental Figure 1. PLS-DA t_1 versus t_2 score plots derived from the analysis to distinguish children with kwashiorkor versus marasmus after nutritional stabilization from stunted community controls. PLS-DA analysis was performed on age- and sex-adjusted concentrations of metabolites. These were measured in serum of children with severe acute malnutrition after nutritional stabilization and in serum of stunted community controls. Asterisks are the centroids of each group. The two main PLS-DA components that capture the variability relating to group classification are represented by t_1 and t_2. Kwa, kwashiorkor; Mara, marasmus; Stt, stunted.



Supplemental Figure 2. Differences in all metabolites measured in children with kwashiorkor or marasmus after nutritional stabilization. Standardized estimates and SEMs were obtained from linear regression models adjusted for age, and sex. Group numbers are as follows: kwashiorkor, n = 21; marasmus, n = 19. Metabolites are ordered based on Pearson hierarchal clustering of all metabolites within each compound class from patients with severe acute malnutrition at admission and after nutritional stabilization. Scaled estimates and SEMs allows the comparison of effect sizes across different metabolites. The direction of the bar indicates which diagnostic group had higher metabolite levels and those that reached FDR-adjusted significance are labelled in dark grey. All metabolite abbreviations are detailed in Supplemental Tables 1-8. Kwa, kwashiorkor; Mara, marasmus.



Supplemental Figure 3. Differences between children with severe acute malnutrition at admission and after nutritional stabilization compared to stunted and non-stunted community controls in levels of total amino acids (A), serotonin (B), tryptophan (C), kynurenine (D), serotonin-to-tryptophan ratio (E) and kynurenine-to-tryptophan ratio (F). Boxplots summarize the median (midline) and interquartile range (upper and lower box). Open circles beyond boxplot whiskers indicate outlying data points. Number in groups are as follows: Admission, n=39; after nutritional stabilization, n=40; stunted, n=78; and non-stunted, n=79 community controls. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; Stab, stabilization; Stt, stunted.

Supplemental Table 1. List of amino acids (n=21) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
Amino Acids	Alanine	Ala	√	√
n=21	Arginine	Arg	√	√
	Asparagine	Asn	√	√
	Aspartate	Asp	√	√
	Citrulline	Cit	√	√
	Glutamine	Gln	√	√
	Glutamate	Glu	√	√
	Glycine	Gly	√	√
	Histidine	His	√	√
	Isoleucine	Ile	√	√
	Leucine	Leu	√	√
	Lysine	Lys	√	√
	Methionine	Met	√	√
	Ornithine	Orn	√	√
	Phenylalanine	Phe	√	√
	Proline	Pro	√	√
	Serine	Ser	√	√
	Threonine	Thr	√	√
	Tryptophan	Trp	√	√
	Tyrosine	Tyr	√	√
	Valine	Val	√	√

[1] Check marks indicates availability of data for each metabolite; the 21 amino acids are available in both the SAM patients and community controls. SAM, severe acute malnutrition.

Supplemental Table 2. List of biogenic amines (n=21) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
Biogenic Amines n=21	Acetylornithine	Ac.Orn	–	–
	Asymmetric dimethylarginine	ADMA	√	√
	a-Aminoadipic acid	alpha.AAA	√	√
	cis-OH-Pro cis-4-Hydroxyproline	c4.OH.Pro	–	–
	Carnosine	Carnosine	–	–
	Creatinine	Creatinine	√	√
	DOPA	DOPA	–	–
	Dopamine	Dopamine	–	–
	Histamine	Histamine	–	–
	Kynurenine	Kynurenine	√	√
	Methioninesulfoxide	Met.SO	–	–
	Nitrotyrosine	Nitro.Tyr	–	–
	Phenylethylamine	PEA	–	–
	Putrescine	Putrescine	–	–
	Symmetric dimethylarginine	SDMA	–	–
	Serotonin	Serotonin	√	√
	Spermidine	Spermidine	√	–
	Spermine	Spermine	√	√
	trans-OH-Pro trans-4-Hydroxyproline	t4.OH.Pro	–	–
	Taurine	Taurine	√	√
	Total Dimethylarginine	total.DMA	–	–

[1] Check marks indicates availability of data for each metabolite; of the 21 biogenic amines, 8 are available in the SAM patients and 7 in the community controls. SAM, severe acute malnutrition.

Supplemental Table 3. List of sphingomyelins (n=15) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites[2]	Symbol	SAM	Controls
Sphingolipids	Hydroxysphingomyelin C14:1	SM (OH) C14:1	√	√
n=15	Hydroxysphingomyelin C16:1	SM (OH) C16:1	√	√
	Hydroxysphingomyelin C22:1	SM (OH) C22:1	√	√
	Hydroxysphingomyelin C22:2	SM (OH) C22:2	√	√
	Hydroxysphingomyelin C24:1	SM (OH) C24:1	√	√
	Sphingomyelin C16:0	SM C16:0	√	√
	Sphingomyelin C16:1	SM C16:1	√	√
	Sphingomyelin C18:0	SM C18:0	√	√
	Sphingomyelin C18:1	SM C18:1	√	√
	Sphingomyelin C20:2	SM C20:2	√	√
	Sphingomyelin C22:3	SM C22:3	√	√
	Sphingomyelin C24:0	SM C24:0	√	√
	Sphingomyelin C24:1	SM C24:1	√	√
	Sphingomyelin C26:0	SM C26:0	√	√
	Sphingomyelin C26:1	SM C26:1	√	√

[1] Check marks indicate availability of data for each metabolite; all 15 sphingomyelins are available in both the SAM patients and community controls. [2] The number of carbons and double bonds that compose a fatty acid is denoted by Cx:y, where x is the number of carbons and y is the number of double bonds. SAM, severe acute malnutrition; SM, sphingomyelin; SM (OH), hydroxysphingomyelin.

Supplemental Table 4. List of acylcarnitines (n=40) that were assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
Acylcarnitines	Carnitine	C0	√	√
n=40	Decanoylcarnitine	C10	–	–
	Decenoylcarnitine	C10:1	–	–
	Decadienylcarnitine	C10:2	–	–
	Dodecanoylcarnitine	C12	–	–
	Dodecenoylcarnitine	C12-DC	–	–
	Dodecanedioylcarnitine	C12:1	–	–
	Tetradecanoylcarnitine	C14	–	–
	Tetradecenoylcarnitine	C14:1	√	–
	Hydroxytetradecenoylcarnitine	C14:1-OH	–	–
	Tetradecadienylcarnitine	C14:2	√	–
	Hydroxytetradecadienylcarnitine	C14:2-OH	–	–
	Hexadecanoylcarnitine	C16	–	–
	Hydroxyhexadecanoylcarnitine	C16-OH	–	–
	Hexadecenoylcarnitine	C16:1	–	–
	Hydroxyhexadecenoylcarnitine	C16:1-OH	–	–
	Hexadecadienylcarnitine	C16:2	–	–
	Hydroxyhexadecadienylcarnitine	C16:2-OH	–	–
	Octadecanoylcarnitine	C18	–	–
	Octadecenoylcarnitine	C18:1	√	√
	Hydroxyoctadecenoylcarnitine	C18:1-OH	–	–
	Octadecadienylcarnitine	C18:2	√	√
	Acetylcarnitine	C2	√	√
	Propionylcarnitine	C3	–	–
	Hydroxybutyrylcarnitine	C4-OH (C3-DC)	√	–
	Hydroxypropionylcarnitine	C3-OH	–	–
	Propenoylcarnitine	C3:1	–	–
	Butyrylcarnitine	C4	–	–
	Butenylcarnitine	C4:1	√	–
	Valerylcarnitine	C5	–	–
	Glutarylcarnitine	C5-DC (C6-OH)	–	–
	Methylglutarylcarnitine	C5-M-DC	–	–
	Hydroxyvalerylcarnitine	C5-OH (C3-DC-M)	–	–
	Tiglylcarnitine	C5:1	–	–
	Glutaconylcarnitine	C5:1-DC	–	–
	Hexanoylcarnitine	C6 (C4:1-DC)	–	–
	Hexenoylcarnitine	C6:1	–	–

	Pimelylcarnitine	C7-DC	–	–
	Octanoylcarnitine	C8	–	–
	Nonaylcarnitine	C9	–	–

[1] Check marks indicates availability of data for each metabolite; of the 40 acylcarnitines, 8 are available in the SAM patients and 4 in the community controls. SAM, severe acute malnutrition.

Supplemental Table 5. List of lysophospholipids (n=14) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites[2]	Symbol	SAM	Controls
Lysophospholipids	Lysophosphatidylcholine acyl C14:0	lysoPC a C14:0	–	–
n=14	Lysophosphatidylcholine acyl C16:0	lysoPC a C16:0	√	√
	Lysophosphatidylcholine acyl C16:1	lysoPC a C16:1	√	√
	Lysophosphatidylcholine acyl C17:0	lysoPC a C17:0	√	√
	Lysophosphatidylcholine acyl C18:0	lysoPC a C18:0	√	√
	Lysophosphatidylcholine acyl C18:1	lysoPC a C18:1	√	√
	Lysophosphatidylcholine acyl C18:2	lysoPC a C18:2	√	√
	Lysophosphatidylcholine acyl C20:3	lysoPC a C20:3	√	√
	Lysophosphatidylcholine acyl C20:4	lysoPC a C20:4	√	√
	Lysophosphatidylcholine acyl C24:0	lysoPC a C24:0	√	√
	Lysophosphatidylcholine acyl C26:0	lysoPC a C26:0	√	√
	Lysophosphatidylcholine acyl C26:1	lysoPC a C26:1	√	√
	Lysophosphatidylcholine acyl C28:0	lysoPC a C28:0	√	√
	Lysophosphatidylcholine acyl C28:1	lysoPC a C28:1	√	√

[1] Check marks indicates availability of data for each metabolite; all 14 lysophospholipids are available in both the SAM patients and community controls. [2] The number of carbons and double bonds that composes a fatty acid is denoted by Cx:y, where x is the number of carbons and y is the number of double bonds. lysoPC, lysophosphatidylcholine; SAM, severe acute malnutrition.

Supplemental Table 6. List of phosphatidylcholine diacyls (n=38) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
Glycerophosphatidylcholine acyl alkyl n=38	Phosphatidylcholine diacyl C24:0	PC aa C24:0	√	√
	Phosphatidylcholine diacyl C26:0	PC aa C26:0	√	–
	Phosphatidylcholine diacyl C28:1	PC aa C28:1	√	√
	Phosphatidylcholine diacyl C30:0	PC aa C30:0	√	√
	Phosphatidylcholine diacyl C30:2	PC aa C30:2	√	√
	Phosphatidylcholine diacyl C32:0	PC aa C32:0	√	√
	Phosphatidylcholine diacyl C32:1	PC aa C32:1	√	√
	Phosphatidylcholine diacyl C32:2	PC aa C32:2	√	√
	Phosphatidylcholine diacyl C32:3	PC aa C32:3	√	√
	Phosphatidylcholine diacyl C34:1	PC aa C34:1	√	√
	Phosphatidylcholine diacyl C34:2	PC aa C34:2	√	√
	Phosphatidylcholine diacyl C34:3	PC aa C34:3	√	√
	Phosphatidylcholine diacyl C34:4	PC aa C34:4	√	√
	Phosphatidylcholine diacyl C36:0	PC aa C36:0	√	√
	Phosphatidylcholine diacyl C36:1	PC aa C36:1	√	√
	Phosphatidylcholine diacyl C36:2	PC aa C36:2	√	√
	Phosphatidylcholine diacyl C36:3	PC aa C36:3	√	√
	Phosphatidylcholine diacyl C36:4	PC aa C36:4	√	√
	Phosphatidylcholine diacyl C36:5	PC aa C36:5	√	√
	Phosphatidylcholine diacyl C36:6	PC aa C36:6	√	√
	Phosphatidylcholine diacyl C38:0	PC aa C38:0	√	√
	Phosphatidylcholine diacyl C38:1	PC aa C38:1	√	√
	Phosphatidylcholine diacyl C38:3	PC aa C38:3	√	√
	Phosphatidylcholine diacyl C38:4	PC aa C38:4	√	√
	Phosphatidylcholine diacyl C38:5	PC aa C38:5	√	√
	Phosphatidylcholine diacyl C38:6	PC aa C38:6	√	√
	Phosphatidylcholine diacyl C40:1	PC aa C40:1	√	–
	Phosphatidylcholine diacyl C40:2	PC aa C40:2	√	√
	Phosphatidylcholine diacyl C40:3	PC aa C40:3	√	√
	Phosphatidylcholine diacyl C40:4	PC aa C40:4	√	√
	Phosphatidylcholine diacyl C40:5	PC aa C40:5	√	√

	Phosphatidylcholine diacyl C40:6	PC aa C40:6	√	√
	Phosphatidylcholine diacyl C42:0	PC aa C42:0	√	√
	Phosphatidylcholine diacyl C42:1	PC aa C42:1	√	√
	Phosphatidylcholine diacyl C42:2	PC aa C42:2	√	√
	Phosphatidylcholine diacyl C42:4	PC aa C42:4	√	√
	Phosphatidylcholine diacyl C42:5	PC aa C42:5	√	√
	Phosphatidylcholine diacyl C42:6	PC aa C42:6	√	√

[1] Check marks indicates availability of data for each metabolite; of the 38 phosphatidylcholine diacyls, 38 are available in the SAM patients and 36 in the community controls. The number of carbons and double bonds that composes a fatty acid is denoted by Cx:y, where x is the number of carbons and y is the number of double bonds and diacyl (aa) indicates that the fatty acids are bound on the glycerol backbone with ester bonds at both the sn-1 and sn-2 positions. PC aa, phosphatidylcholine diacyl; SAM, severe acute malnutrition.

Supplemental Table 7. List of phosphatidylcholine acyl alkyls (n=38) assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
	Phosphatidylcholine acyl-alkyl C30:0	PC ae C30:0	√	–
Phosphatidylcholine diacyl	Phosphatidylcholine acyl-alkyl C30:1	PC ae C30:1	√	√
n=38	Phosphatidylcholine acyl-alkyl C30:2	PC ae C30:2	√	√
	Phosphatidylcholine acyl-alkyl C32:1	PC ae C32:1	√	√
	Phosphatidylcholine acyl-alkyl C32:2	PC ae C32:2	√	√
	Phosphatidylcholine acyl-alkyl C34:0	PC ae C34:0	√	√
	Phosphatidylcholine acyl-alkyl C34:1	PC ae C34:1	√	√
	Phosphatidylcholine acyl-alkyl C34:2	PC ae C34:2	√	√
	Phosphatidylcholine acyl-alkyl C34:3	PC ae C34:3	√	√
	Phosphatidylcholine acyl-alkyl C36:0	PC ae C36:0	√	√
	Phosphatidylcholine acyl-alkyl C36:1	PC ae C36:1	√	√
	Phosphatidylcholine acyl-alkyl C36:2	PC ae C36:2	√	√
	Phosphatidylcholine acyl-alkyl C36:3	PC ae C36:3	√	√
	Phosphatidylcholine acyl-alkyl C36:4	PC ae C36:4	√	√
	Phosphatidylcholine acyl-alkyl C36:5	PC ae C36:5	√	√
	Phosphatidylcholine acyl-alkyl C38:0	PC ae C38:0	√	√
	Phosphatidylcholine acyl-alkyl C38:1	PC ae C38:1	√	√
	Phosphatidylcholine acyl-alkyl C38:2	PC ae C38:2	√	√

Phosphatidylcholine acyl-alkyl C38:3	PC ae C38:3	√	√
Phosphatidylcholine acyl-alkyl C38:4	PC ae C38:4	√	√
Phosphatidylcholine acyl-alkyl C38:5	PC ae C38:5	√	√
Phosphatidylcholine acyl-alkyl C38:6	PC ae C38:6	√	√
Phosphatidylcholine acyl-alkyl C40:1	PC ae C40:1	√	√
Phosphatidylcholine acyl-alkyl C40:2	PC ae C40:2	√	√
Phosphatidylcholine acyl-alkyl C40:3	PC ae C40:3	√	√
Phosphatidylcholine acyl-alkyl C40:4	PC ae C40:4	√	√
Phosphatidylcholine acyl-alkyl C40:5	PC ae C40:5	√	√
Phosphatidylcholine acyl-alkyl C40:6	PC ae C40:6	√	√
Phosphatidylcholine acyl-alkyl C42:0	PC ae C42:0	–	–
Phosphatidylcholine acyl-alkyl C42:1	PC ae C42:1	√	√
Phosphatidylcholine acyl-alkyl C42:2	PC ae C42:2	√	√
Phosphatidylcholine acyl-alkyl C42:3	PC ae C42:3	√	√
Phosphatidylcholine acyl-alkyl C42:4	PC ae C42:4	√	√
Phosphatidylcholine acyl-alkyl C42:5	PC ae C42:5	√	√
Phosphatidylcholine acyl-alkyl C44:3	PC ae C44:3	√	√
Phosphatidylcholine acyl-alkyl C44:4	PC ae C44:4	√	√
Phosphatidylcholine acyl-alkyl C44:5	PC ae C44:5	√	√
Phosphatidylcholine acyl-alkyl C44:6	PC ae C44:6	√	√

[1] Check marks indicates availability of data for each metabolite; of the 38 phosphatidylcholine acyl alkyls, 37 are available in the SAM patients and 36 in the community controls. The number of carbons and double bonds that composes a fatty acid is denoted by Cx:y, where x is the number of carbons and y is the number of double bonds and acyl-alkyl (ae) indicates that the fatty acids are bound on the glycerol backbone with an ether bond at the sn-1 position. PC ae, phosphatidylcholine acyl alkyls; SAM, severe acute malnutrition.

Supplemental Table 8. List of electrolytes and other biochemical variables assessed in the serum of patients with severe acute malnutrition and community controls.

			Data Availablility[1]	
	Metabolites	Symbol	SAM	Controls
Electrolytes and other biochemical variables	Sum of Hexoses (including Glucose)	Sugars	√	–
	Sodium	Sodium	√	–
	Potassium	Potassium	√	–
	Phosphate	Phosphate	√	–
	Magnesium	Magnesium	√	–
	Albumin	Albumin	√	–

[1] Check marks indicate availability of data for each metabolite; the six electrolytes and other biochemical variables were assessed only in the SAM patients. SAM, severe acute malnutrition.

Supplemental Table 9. Serum concentrations of amino acids[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Amino Acids µmol/L	All SAM n=39 Mean±SD	Kwas n=21 Mean±SD	Mara n=18 Mean±SD	All SAM n=40 Mean±SD	Kwa n=21 Mean±SD	Mara n=19 Mean±SD	Stt (n=78) Mean±SD	nStt (n=79) Mean±SD
Ala	241±148	240±141	242±160	449±267	425±271	475±267	505±125	534±122
Arg	48.0±19.1	43.3±16.7	53.6±20.7	90.6±39.3	86.5±37.5	95.1±41.8	81.0±23.6	92.2±26.3
Asn	41.4±13.4	38.1±13.1	45.1±13.0	68.6±31.1	70.6±33.0	66.5±29.7	68.4±20.0	75.1±18.8
Asp	20.2±13.0	15.6±10.2	25.6±14.0	26.8±17.4	27.3±15.7	26.2±19.5	60.0±23.8	58.4±19.6
Cit	6.66±3.29	5.94±2.66	7.49±3.80	10.9±7.8	10.6±8.2	11.1±7.6	21.2±8.7	23.6±7.1
Gln	380±266	286±170	491±317	617±320	643±396	589±215	524±139	564±136
Glu	68.3±37.6	60.3±32.3	77.7±41.9	102±44	106±33	98.2±55.3	259±127	309±116
Gly	284±164	255±115	319±205	341±127	356±130	324±124	336±103	369±100
His	93.8±21.8	95.4±22.5	92.0±21.5	117±37	131±43	102±20.6	93.2±24.8	104±23
Ile	32.4±13.9	30.7±11.8	34.5±16.2	71.3±34.2	74.7±36.5	67.6±32.0	58.8±17.8	66.8±21.0
Leu	49.3±21.0	43.8±15.8	55.7±24.6	101±52	105±58	96.8±45.3	139±45	157±50
Lys	113±41	96.7±26.3	132±48	198±108	180±87	219±126	151±57	180±53
Met	12.8±4.9	10.7±3.6	15.2±5.1	19.2±11.7	18.2±12.9	20.4±10.5	23.3±7.4	27.9±8.8
Orn	23.8±20.1	21.6±24.5	26.3±13.5	54.8±41.6	57.9±43.3	51.3±40.6	94.9±54.9	112±55
Phe	70.4±28.9	64.0±30.1	78.0±26.3	78.2±34.5	79.3±40.6	77.0±27.2	91.0±20.2	91.0±16.2
Pro	211±103	181±69	247±125	335±158	333±175	337±140	194±57	198±46
Ser	132±80	129±93	136±63	179±85	200±103	155±52	177±56	196±58
Thr	51.7±30.3	36.3±16.0	69.7±33.5	101±56	106±60	95.9±51.7	93.7±33.8	111±34
Trp	8.34±8.72	4.87±3.71	12.4±11.0	17.8±11.7	13.8±9.0	22.2±12.9	37.0±17.6	45.6±18.2
Tyr	26.7±15.0	22.6±14.3	31.4±14.9	44.8±29.0	41.3±31.5	48.7±26.2	61.5±17.2	66.0±16.1
Val	79.1±30.9	73.1±24.9	86.0±36.1	166±76	180±88	150±59	150±40	167±43

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 1. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 10. Group differences in serum concentrations of amino acids[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Amino Acids	SAM			Admission									Stabilization											
µmol/L	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]	Est.	SE	P[2]
Ala	1.06	0.23	<0.01	0.02	0.37	0.96	1.66	0.12	<0.01	1.75	0.12	<0.01	0.47	0.45	0.39	-0.81	0.14	<0.01	0.69	0.14	<0.01	0.64	0.13	<0.01
Arg	1.46	0.20	<0.01	0.55	0.33	0.15	1.44	0.15	<0.01	1.65	0.15	<0.01	0.40	0.37	0.36	-0.47	0.16	0.07	0.81	0.16	<0.01	0.03	0.15	0.81
Asn	1.20	0.22	<0.01	0.41	0.27	0.12	1.41	0.14	<0.01	1.63	0.14	<0.01	0.09	0.40	0.86	-0.85	0.16	<0.01	0.24	0.16	0.15	0.30	0.15	0.07
Asp	0.46	0.16	<0.05	0.90	0.30	<0.01	1.77	0.13	<0.01	1.73	0.13	<0.01	0.06	0.28	0.86	-0.92	0.12	<0.01	0.28	0.12	0.01	1.30	0.11	0.01
Cit	0.55	0.18	<0.01	0.29	0.24	0.21	1.44	0.11	<0.01	1.93	0.11	<0.01	0.15	0.33	0.73	-0.77	0.13	<0.01	0.18	0.13	0.01	1.28	0.12	0.01
Gln	1.28	0.23	<0.01	0.11	0.41	0.76	1.44	0.16	<0.01	1.29	0.16	<0.01	0.03	0.40	0.95	-0.99	0.15	<0.01	0.10	0.15	0.58	0.09	0.14	0.57
Glu	0.60	0.12	<0.01	0.29	0.23	0.19	1.49	0.11	<0.01	2.08	0.11	<0.01	0.15	0.18	0.49	-0.91	0.10	<0.01	0.09	0.10	0.31	1.39	0.10	0.01
Gly	0.66	0.21	<0.01	0.45	0.46	0.33	1.01	0.18	<0.01	0.97	0.18	<0.01	0.04	0.36	0.76	-0.50	0.17	<0.01	0.03	0.17	0.85	0.19	0.15	0.19
His	0.69	0.20	<0.01	-0.09	0.29	0.76	0.04	0.17	0.83	0.38	0.17	0.05	0.58	0.43	0.25	-0.65	0.19	<0.01	0.29	0.19	0.12	0.47	0.17	0.05
Ile	1.58	0.20	<0.01	0.09	0.31	0.78	1.44	0.13	<0.01	1.67	0.13	<0.01	0.02	0.42	0.97	-0.71	0.15	<0.01	0.08	0.15	0.66	0.04	0.14	0.72

	1.	0.	<0.	0.3	0.	0.2	1.9	0.	<0.	2.	0.	<0.	0.1	0.	0.	0.7	0.	<0.	0.9	0.	<0.		0.	<0.
Leu	16	17	01	1	22	2	3	11	01	14	11	01	3	35	77	5	13	01	8	13	01	0.87	12	01
																-								
	1.	0.	<0.	0.6	0.	<0.	0.7	0.	<0.	1.	0.	<0.	0.6	0.	0.	0.3	0.	<0.	0.0	0.	0.9	-	0.	0.3
Lys	16	22	01	5	25	05	9	15	01	16	14	01	7	41	17	9	17	05	0	17	9	0.19	16	2
	0.	0.	<0.	0.6	0.	<0.	1.3	0.	<0.	1.	0.	<0.	0.5	0.	0.	0.6	0.	<0.	1.0	0.	<0.		0.	<0.
Met	69	20	01	4	25	05	8	13	01	73	13	01	9	38	19	6	16	01	4	15	01	0.85	14	01
	0.	0.	<0.	0.5	0.	0.1	1.8	0.	<0.	1.	0.	<0.	0.0	0.	0.	0.8	0.	<0.	1.0	0.	<0.		0.	<0.
Orn	95	19	01	0	26	0	2	12	01	99	12	01	6	31	88	6	13	01	4	13	01	0.96	12	01
	0.	0.	0.2	0.6	0.	0.1	1.0	0.	<0.	1.	0.	<0.	0.3	0.	0.	0.6	0.	<0.	0.7	0.	<0.		0.	<0.
Phe	35	25	4	9	44	7	6	16	01	04	16	01	8	42	45	8	16	01	0	16	01	0.69	15	01
							-									-			-					
	0.	0.	<0.	0.4	0.	0.1	0.1	0.	0.6	0.	0.	0.9	0.3	0.	0.	0.9	0.	<0.	0.8	0.	<0.	-	0.	<0.
Pro	85	17	01	9	28	3	0	18	4	02	18	3	0	34	46	8	19	01	4	19	01	0.91	17	01
													-											
	0.	0.	<0.	0.3	0.	0.5	1.0	0.	<0.	1.	0.	<0.	0.4	0.	0.	0.1	0.	0.3	0.3	0.	<0.		0.	0.1
Ser	88	24	01	3	42	2	4	17	01	24	17	01	4	35	29	6	16	9	8	16	05	0.27	14	0
	1.	0.	<0.	1.2	0.	<0.	1.3	0.	<0.	1.	0.	<0.	0.0	0.	0.	0.1	0.	0.4	0.4	0.	<0.		0.	0.0
Thr	22	23	01	3	29	01	5	14	01	64	14	01	9	45	87	3	15	7	4	15	01	0.29	14	7
	0.	0.	<0.	0.8	0.	<0.	1.8	0.	<0.	2.	0.	<0.	0.5	0.	0.	0.9	0.	<0.	1.2	0.	<0.		0.	<0.
Trp	90	12	01	1	23	01	9	12	01	13	12	01	3	25	07	8	11	01	2	11	01	1.10	11	01
	0.	0.	<0.	0.7	0.	0.0	1.7	0.	<0.	1.	0.	<0.	0.6	0.	0.	0.8	0.	<0.	1.0	0.	<0.		0.	<0.
Tyr	87	21	01	0	32	5	5	12	01	88	12	01	9	38	12	5	13	01	0	13	01	0.93	12	01
													-											
	1.	0.	<0.	0.3	0.	0.3	1.6	0.	<0.	1.	0.	<0.	0.1	0.	0.	0.0	0.	0.9	0.2	0.	0.1		0.	0.4
Val	61	20	01	0	27	5	3	12	01	85	12	01	7	42	74	1	15	7	4	15	5	0.13	13	2

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 1. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 11. Serum concentrations of biogenic amines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Biogenic Amines	All SAM	Kwas	Mara	All SAM	Kwa	Mara	Stt	nStt
µmol/L	n=39	n=21	n=18	n=40	n=21	n=19	(n=78)	(n=79)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
ADMA	0.3±0.4	0.21±0.23	0.42±0.52	0.53±0.34	0.47±0.37	0.59±0.28	0.99±0.30	1.06±0.28
alpha.AAA	0.6±0.4	0.51±0.32	0.71±0.54	1.30±0.97	1.23±0.67	1.38±1.24	3.34±4.15	1.86±2.81
Creatinine	32.0±20.4	32.6±22.0	31.3±18.9	35.7±17.3	35.9±15.7	35.4±19.3	21.6±7.4	23.0±7.1
Kynurenine	1.51±1.38	0.91±0.81	2.21±1.58	2.99±1.73	2.46±1.53	3.59±1.79	2.98±1.33	2.94±1.01
Serotonin	0.72±0.81	0.73±0.96	0.70±0.63	0.80±0.80	0.72±0.86	0.89±0.75	1.37±0.77	1.58±0.65
Spermidine	0.39±0.32	0.39±0.36	0.40±0.27	0.35±0.28	0.37±0.34	0.33±0.21	–	–
Spermine	0.27±0.20	0.26±0.20	0.27±0.21	0.22±0.12	0.23±0.12	0.21±0.11	0.11±0.08	0.11±0.07
Taurine	92.9±43.8	85.5±44.2	102±43	94.8±46.4	94.1±50.9	95.6±42.3	177±56	209±56

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 2. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 12. Group differences in serum concentrations of biogenic amines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Biogenic Amines µmol/L	SAM			Admission									Stabilization											
	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]
ADMA	0.66	0.19	<0.01	0.38	0.31	0.30	1.82	0.12	<0.01	1.91	0.12	<0.01	0.30	0.29	0.39	1.16	0.11	<0.01	1.25	0.11	<0.01	1.20	0.10	<0.01
alpha.AAA	0.53	0.09	<0.01	0.23	0.13	0.14	1.04	0.20	<0.01	0.62	0.20	<0.01	-0.02	0.19	0.94	0.51	0.20	<0.05	0.09	0.20	0.72	0.29	0.18	0.16
Creatinine	0.35	0.17	0.08	-0.26	0.40	0.60	-0.85	0.17	<0.01	-0.63	0.17	<0.01	-0.25	0.38	0.58	-1.19	0.17	<0.01	-0.97	0.16	<0.01	-1.08	0.15	<0.01
Kynurenine	1.18	0.19	<0.01	1.06	0.32	<0.01	1.37	0.16	<0.01	1.34	0.16	<0.01	0.65	0.37	0.13	0.17	0.16	0.36	0.15	0.16	0.41	0.16	0.14	0.34
Serotonin	0.10	0.11	0.45	-0.18	0.35	0.68	0.98	0.16	<0.01	1.25	0.16	<0.01	-0.04	0.32	0.93	0.85	0.16	<0.01	1.11	0.16	<0.01	0.98	0.15	<0.01
Spermidine	-0.14	0.20	0.55	-0.04	0.37	0.94		–			–		-0.20	0.32	0.61		–			–			–	
Spermine	-0.32	0.24	0.27	-0.11	0.48	0.86	-1.15	0.16	<0.01	-1.26	0.16	<0.01	-0.12	0.31	0.75	-0.85	0.14	<0.01	-0.94	0.14	<0.01	-0.90	0.13	<0.01
Taurine	0.04	0.15	0.85	0.33	0.28	0.32	1.19	0.16	<0.01	1.35	0.16	<0.01	-0.01	0.28	0.98	1.18	0.16	<0.01	1.33	0.15	<0.01	1.26	0.14	<0.01

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 2. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 13. Serum concentrations of sphingolipids[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Sphingolipids	All SAM	Kwas	Mara	All SAM	Kwa	Mara	Stt	nStt
µmol/L	n=39	n=21	n=18	n=40	n=21	n=19	(n=78)	(n=79)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
SM (OH) C14:1	1.86±0.77	1.81±0.76	1.92±0.81	1.95±0.69	1.93±0.68	1.98±0.72	2.48±0.86	2.51±0.72
SM (OH) C16:1	1.42±0.52	1.29±0.42	1.58±0.60	1.30±0.53	1.35±0.59	1.24±0.45	2.11±0.72	2.16±0.59
SM (OH) C22:1	3.22±1.79	2.81±1.58	3.69±1.94	3.85±1.81	3.37±1.72	4.37±1.80	7.51±2.33	7.55±1.82
SM (OH) C22:2	2.02±0.92	1.88±0.96	2.17±0.88	2.23±1.07	2.26±1.15	2.19±1.00	4.61±1.44	4.89±1.03
SM (OH) C24:1	0.59±0.35	0.53±0.31	0.65±0.39	0.69±0.33	0.65±0.33	0.72±0.33	0.87±0.26	0.88±0.23
SM C16:0	82.2±26.5	77.6±22.8	87.6±30.1	80.0±24.3	76.8±23.8	83.5±25.0	97.5±28.1	97.3±23.4
SM C16:1	10.1±4.3	10.0±4.3	10.1±4.4	9.64±4.34	9.67±3.92	9.61±4.88	9.13±2.60	9.41±2.23
SM C18:0	16.1±7.4	14.9±4.1	17.4±9.9	16.1±8.3	15.5±8.5	16.8±8.2	19.6±7.5	20.1±5.4
SM C18:1	5.76±2.43	5.72±2.13	5.8±2.8	5.25±2.57	5.38±2.95	5.10±2.16	6.57±2.33	6.86±1.63
SM C20:2	0.25±0.14	0.24±0.13	0.27±0.15	0.32±0.22	0.31±0.22	0.34±0.22	0.58±0.20	0.55±0.16
SM C22:3	1.09±0.71	0.9±0.51	1.31±0.84	1.09±0.83	1.10±0.88	1.09±0.80	6.12±2.39	5.77±1.45
SM C24:0	10.7±5.8	9.9±5.0	11.7±6.6	12.8±5.43	11.9±5.7	13.7±5.1	21.4±6.3	21.1±4.7
SM C24:1	24.8±11.7	21.7±8.3	28.4±14.0	26.4±11.1	23.7±8.0	29.3±13.4	40.5±11.5	40.7±8.1
SM C26:0	0.18±0.11	0.17±0.11	0.19±0.11	0.17±0.08	0.16±0.09	0.18±0.07	0.20±0.06	0.20±0.05
SM C26:1	0.18±0.09	0.18±0.09	0.19±0.08	0.21±0.11	0.19±0.11	0.22±0.11	0.28±0.11	0.27±0.08

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 3. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 14. Group differences in serum concentrations of sphingolipids[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Sphingolipids	SAM			Admission									Stabilization											
µmol/L	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2	Est.	SE M	P^2
SM (OH)		0.1		0.3	0.3	0.4		0.1	<0.0		0.1	<0.0		0.3	0.7	0.7	0.1	<0.0	0.7	0.1	<0.0	0.7	0.1	<0.0
C14:1	0.15	8	0.49	7	7	1	0.91	8	1	0.93	8	1	0.14	4	3	6	7	1	8	7	1	7	5	1
SM (OH)	-	0.1		0.5	0.2	0.1		0.1	<0.0		0.1	<0.0	-	0.3	0.6	1.3	0.1	<0.0	1.3	0.1	<0.0	1.3	0.1	<0.0
C16:1	0.24	8	0.25	1	9	3	1.07	6	1	1.14	6	1	0.17	1	5	1	6	1	8	6	1	5	4	1
SM (OH)		0.1		0.6	0.3	0.0		0.1	<0.0		0.1	<0.0		0.2	0.0	1.3	0.1	<0.0	1.4	0.1	<0.0	1.3	0.1	<0.0
C22:1	0.33	5	0.06	1	1	9	1.70	3	1	1.74	2	1	0.62	9	6	6	2	1	0	2	1	8	1	1
SM (OH)		0.1		0.3	0.2	0.3		0.1	<0.0		0.1	<0.0		0.2	0.7	1.4	0.1	<0.0	1.6	0.1	<0.0	1.5	0.1	<0.0
C22:2	0.18	4	0.29	3	8	2	1.64	2	1	1.80	2	1	0.09	7	9	6	2	1	3	2	1	5	1	1
SM (OH)		0.2		0.6	0.4	0.1		0.1	<0.0		0.1	<0.0		0.4	0.4	0.6	0.1	<0.0	0.7	0.1	<0.0	0.6	0.1	<0.0
C24:1	0.37	3	0.18	2	0	9	1.03	7	1	1.08	7	1	0.34	0	8	7	7	1	1	6	1	9	5	1
	-	0.2		0.4	0.3	0.2		0.1	<0.0		0.1	<0.0		0.3	0.3	0.8	0.1	<0.0	0.7	0.1	<0.0	0.7	0.1	<0.0
SM C16:0	0.10	2	0.71	6	7	8	0.71	8	1	0.67	7	1	0.37	7	9	0	8	1	7	7	1	9	6	1
	-	0.2		0.2	0.4	0.7	-	0.1		-	0.1			0.4	0.7	0.0	0.1		0.1	0.1		0.0	0.1	
SM C16:1	0.16	0	0.50	1	4	1	0.14	8	0.50	0.05	8	0.83	0.22	7	1	2	9	0.94	2	8	0.58	7	7	0.73
	-	0.2		0.1	0.3	0.6		0.1	<0.0		0.1	<0.0		0.4	0.8	0.7	0.1	<0.0	0.8	0.1	<0.0	0.7	0.1	<0.0
SM C18:0	0.09	2	0.75	8	5	7	0.65	7	1	0.72	6	1	0.10	1	5	4	8	1	2	7	1	8	6	1
	-	0.1		0.0	0.3	0.9		0.1	<0.0		0.1	<0.0	-	0.4	0.9	0.7	0.1	<0.0	0.9	0.1	<0.0	0.8	0.1	<0.0
SM C18:1	0.29	9	0.19	6	8	0	0.44	8	5	0.61	7	1	0.05	2	2	5	8	1	2	8	1	4	6	1
		0.1		0.2	0.2	0.2		0.1	<0.0		0.1	<0.0		0.3	0.7	1.2	0.1	<0.0	1.1	0.1	<0.0	1.1	0.1	<0.0
SM C20:2	0.30	6	0.11	9	3	8	1.52	4	1	1.41	4	1	0.16	5	1	2	6	1	0	5	1	6	4	1
	-	0.0		0.3	0.1	0.1		0.0	<0.0		0.0	<0.0		0.2	0.9	1.9	0.0	<0.0	1.8	0.0	<0.0	1.9	0.0	<0.0
SM C22:3	0.03	8	0.81	1	7	2	1.90	9	1	1.86	9	1	0.00	0	9	2	9	1	8	9	1	0	8	1
		0.1	<0.0	0.4	0.3	0.2		0.1	<0.0		0.1	<0.0		0.3	0.1	1.2	0.1	<0.0	1.2	0.1	<0.0	1.2	0.1	<0.0
SM C24:0	0.41	8	5	8	5	5	1.64	3	1	1.64	3	1	0.56	3	5	2	3	1	2	3	1	2	2	1
		0.2		0.5	0.3	0.2		0.1	<0.0		0.1	<0.0		0.3	0.2	1.2	0.1	<0.0	1.2	0.1	<0.0	1.2	0.1	<0.0
SM C24:1	0.17	2	0.50	1	6	3	1.41	4	1	1.43	4	1	0.46	5	8	1	4	1	5	4	1	3	3	1
	-	0.2		0.4	0.5	0.4		0.1			0.1			0.3	0.6	0.4	0.1	<0.0	0.4	0.1	<0.0	0.4	0.1	<0.0
SM C26:0	0.12	8	0.73	8	1	3	0.35	9	0.11	0.31	9	0.16	0.23	8	1	9	7	1	4	7	5	6	5	1
		0.1		0.2	0.3	0.4		0.1	<0.0		0.1	<0.0		0.3	0.1	0.7	0.1	<0.0	0.7	0.1	<0.0	0.7	0.1	<0.0
SM C26:1	0.26	8	0.23	9	0	2	1.01	7	1	0.93	7	1	0.55	5	9	8	8	1	1	8	1	4	6	1

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 3. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 15. Serum concentrations of acylcarnitines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Acyl Carnitines	All SAM	Kwas	Mara	All SAM	Kwa	Mara	Stt	nStt
µmol/L	n=39	n=21	n=18	n=40	n=21	n=19	(n=78)	(n=79)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
C0	24.8±11.0	23.0±11.6	26.8±10.4	32.6±14.1	27.8±11.6	37.9±14.9	23.7±7.9	27.39±9.41
C2	11.0±13.1	5.9±4.9	17.0±16.8	13.1±13.0	13.0±14.0	13.1±12.1	5.23±3.30	6.07±3.14
C4-OH (C3-DC)	0.26±0.23	0.23±0.16	0.28±0.29	0.29±0.24	0.37±0.30	0.20±0.12	–	–
C4:1	0.05±0.02	0.04±0.01	0.06±0.03	0.05±0.02	0.05±0.02	0.05±0.02	–	–
C14:1	0.06±0.03	0.05±0.03	0.07±0.03	0.07±0.04	0.07±0.04	0.06±0.04	–	–
C14:2	0.04±0.02	0.03±0.02	0.05±0.02	0.04±0.02	0.04±0.02	0.04±0.02	–	–
C18:1	0.10±0.04	0.09±0.04	0.13±0.03	0.12±0.06	0.12±0.06	0.11±0.05	0.14±0.06	0.16±0.06
C18:2	0.05±0.02	0.05±0.02	0.06±0.02	0.06±0.03	0.06±0.03	0.06±0.03	0.11±0.04	0.11±0.04

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 4. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 16. Group differences in serum concentrations of acylcarnitines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Acyl Carnitines	SAM			Admission									Stabilization											
µmol/L	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]
C0	0.71	0.2 1	<0.01	0.32	0.47	0.53	0.14	0.17	0.48	0.42	0.17	5	0.63	0.39	0.17	0.57	0.17	0.01	0.29	0.16	0.12	0.42	0.15	0.05
C2	0.33	0.23	0.23	0.89	0.41	0.06	-0.44	0.15	<0.01	-0.32	0.15	0.06	-0.07	0.43	0.90	-0.77	0.15	<0.01	-0.64	0.15	<0.01	-0.70	0.14	<0.01
C4-OH (C3-DC)	0.17	0.2 2	0.51	0.23	0.34	0.57		–			–		-0.74	0.35	0.07		–			–			–	
C4:1	-0.09	0.2 1	0.73	0.41	0.33	0.29		–			–		-0.10	0.32	0.80		–			–			–	
C14:1	0.14	0.2 2	0.57	0.64	0.27	<0.05		–			–		-0.19	0.38	0.70		–			–			–	
C14:2	-0.01	0.2 1	0.98	0.65	0.29	0.06		–			–		-0.34	0.36	0.43		–			–			–	
C18:1	0.26	0.2 2	0.26	0.67	0.23	<0.05	0.86	0.17	<0.01	0.98	0.16	<0.01	-0.45	0.34	0.27	0.60	0.17	<0.01	0.72	0.17	<0.01	0.67	0.16	<0.01
C18:2	0.09	0.1 1	0.47	0.31	0.17	0.11	1.34	0.15	<0.01	1.37	0.15	<0.01	-0.09	0.21	0.73	1.26	0.16	<0.01	1.29	0.15	<0.01	1.28	0.14	<0.01

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 4. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 17. Serum concentrations of lysophosphatidylcholines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Lyso-phosphatidylcholine µmol/L	All SAM n=39 Mean±SD	Kwas n=21 Mean±SD	Mara n=18 Mean±SD	All SAM n=40 Mean±SD	Kwa n=21 Mean±SD	Mara n=19 Mean±SD	Stt (n=78) Mean±SD	nStt (n=79) Mean±SD
LysoPC a C16:0	37.0±23.0	29.0±18.2	46.2±24.9	57.5±33.5	47.1±32.6	69.0±31.4	185±91	207±72
LysoPC a C16:1	0.95±0.50	0.97±0.51	0.94±0.49	1.68±1.18	1.39±0.82	2.01±1.43	3.42±1.48	3.66±1.32
LysoPC a C17:0	0.59±0.31	0.49±0.21	0.71±0.36	0.74±0.38	0.63±0.36	0.86±0.36	2.94±1.63	3.27±1.16
LysoPC a C18:0	11.6±7.0	9.52±5.13	14.0±8.2	19.2±11.7	14.9±8.81	23.9±12.8	59.0±31.6	70.6±26.6
LysoPC a C18:1	13.1±6.6	11.5±5.2	15.0±7.7	23.0±14.7	21.3±16.6	24.8±12.4	22.5±8.8	24.5±6.6
LysoPC a C18:2	23.1±12.2	19.1±9.3	27.7±13.8	36.3±28.1	29.5±23.1	43.7±31.7	22.9±9.5	25.1±8.9
LysoPC a C20:3	1.67±0.78	1.49±0.58	1.88±0.93	2.90±1.63	2.43±1.15	3.43±1.94	2.66±1.20	3.12±0.96
LysoPC a C20:4	5.37±4.09	4.33±2.23	6.58±5.35	5.72±3.95	4.55±2.95	7.01±4.57	12.1±5.7	14.2±4.5
LysoPC a C24:0	0.51±0.20	0.47±0.15	0.55±0.25	0.54±0.21	0.50±0.20	0.58±0.22	0.40±0.10	0.41±0.1
LysoPC a C26:0	1.06±0.52	0.98±0.46	1.16±0.58	1.27±0.53	1.21±0.53	1.34±0.55	0.56±0.21	0.49±0.18
LysoPC a C26:1	0.33±0.14	0.32±0.14	0.35±0.14	0.35±0.15	0.34±0.14	0.37±0.15	0.30±0.09	0.28±0.09
LysoPC a C28:0	0.90±0.35	0.86±0.32	0.94±0.39	1.15±0.45	1.1±0.49	1.20±0.41	0.46±0.14	0.45±0.1
LysoPC a C28:1	0.63±0.26	0.57±0.22	0.71±0.28	0.77±0.35	0.73±0.41	0.82±0.27	0.47±0.11	0.49±0.12

[1]Data are presented as mean ± SDs. [2]Metabolites ordered alphabetically. [3]Metabolite abbreviations are detailed in Supplementary Table 5. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 18. Group differences in serum concentrations of lysophosphatidylcholines[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted

Lyso-phophatidylcholine	SAM			Admission									Stabilization											
	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
		SE			SE			SE			SE			SE			SE			SE			SE	
µmol/L	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]	Est.	M	P[2]
	0.4	0.1	<0.0	0.4	0.2	0.0		0.1	<0.0		0.1	<0.0	0.4	0.2	0.0		0.1	<0.0		0.1	<0.0		0.1	<0.0
LysoPC a C16:0	4	2	1	7	2	6	1.86	0	1	1.99	0	1	9	5	9	1.42	1	1	1.54	1	1	1.48	0	1
	0.5	0.1	<0.0	0.0	0.1	0.8		0.1	<0.0		0.1	<0.0	0.4	0.2	0.1		0.1	<0.0		0.1	<0.0		0.1	<0.0
LysoPC a C16:1	5	4	1	5	8	1	1.69	3	1	1.84	3	1	6	9	7	1.14	4	1	1.28	4	1	1.21	3	1
	0.1	0.0	<0.0	0.2	0.1	0.0		0.1	<0.0		0.1	<0.0	0.2	0.1	0.1		0.1	<0.0		0.1	<0.0		0.1	<0.0
LysoPC a C17:0	5	6	5	6	1	5	1.70	2	1	1.88	2	1	1	3	5	1.55	2	1	1.73	2	1	1.64	1	1
	0.4	0.1	<0.0	0.3	0.2	0.1		0.1	<0.0		0.1	<0.0	0.5	0.2	0.0		0.1	<0.0		0.1	<0.0		0.1	<0.0
LysoPC a C18:0	9	1	1	6	1	5	1.83	1	1	2.04	1	1	0	2	5	1.34	1	1	1.54	1	1	1.44	0	1
	0.9	0.2	<0.0	0.5	0.3	0.1		0.1	<0.0		0.1	<0.0	0.5	0.4	0.2		0.1			0.1	<0.0		0.1	
LysoPC a C18:1	0	3	1	4	2	5	1.11	6	1	1.33	6	1	7	4	7	0.22	7	0.29	0.42	7	5	0.32	6	0.07
	0.6	0.2	<0.0	0.7	0.3	0.0		0.1			0.1		0.6	0.4	0.2	-	0.1	<0.0	-	0.1		-	0.1	<0.0
LysoPC a C18:2	2	5	5	7	5	6	0.10	7	0.63	0.31	7	0.11	1	6	7	0.50	9	5	0.32	9	0.13	0.41	7	5
	1.0	0.2	<0.0	0.4	0.2	0.1		0.1	<0.0		0.1	<0.0	0.6	0.3	0.1	-	0.1			0.1			0.1	
LysoPC a C20:3	0	0	1	6	4	0	0.93	7	1	1.32	7	1	6	7	2	0.06	8	0.79	0.32	8	0.12	0.13	7	0.50
	0.0	0.1		0.4	0.2	0.1		0.1	<0.0		0.1	<0.0	0.4	0.3	0.2		0.1	<0.0		0.1	<0.0		0.1	<0.0
LysoPC a C20:4	1	4	0.95	4	5	4	1.34	3	1	1.60	3	1	3	0	3	1.32	3	1	1.58	3	1	1.45	2	1
	0.1	0.2		0.4	0.4	0.4	-	0.1	<0.0	-	0.1	<0.0	0.4	0.4	0.3	-	0.1	<0.0	-	0.1	<0.0	-	0.1	<0.0
LysoPC a C24:0	6	7	0.62	3	5	2	0.73	7	1	0.64	6	1	7	5	8	0.91	7	1	0.81	6	1	0.86	5	1
	0.4	0.2		0.3	0.3	0.4	-	0.1	<0.0	-	0.1	<0.0	0.2	0.3	0.5	-	0.1	<0.0	-	0.1	<0.0	-	0.1	<0.0
LysoPC a C26:0	3	1	0.08	4	5	1	1.17	3	1	1.34	3	1	2	3	8	1.61	2	1	1.78	2	1	1.70	1	1
	0.1	0.2		0.3	0.4	0.5	-	0.1		-	0.1	<0.0	0.0	0.4	0.9	-	0.1	<0.0	-	0.1	<0.0	-	0.1	<0.0
LysoPC a C26:1	6	6	0.62	0	3	7	0.30	8	0.13	0.44	8	5	7	4	0	0.47	8	5	0.62	8	1	0.55	6	1
	0.6	0.2	<0.0	0.2	0.3	0.5	-	0.1	<0.0	-	0.1	<0.0	0.3	0.3	0.3	-	0.1	<0.0	-	0.1	<0.0	-	0.1	<0.0
LysoPC a C28:0	0	1	5	2	1	7	1.24	1	1	1.29	1	1	9	5	5	1.85	1	1	1.89	1	1	1.87	0	1
	0.5	0.3		0.6	0.3	0.1	-	0.1	<0.0	-	0.1	<0.0	0.5	0.4	0.3	-	0.1	<0.0	-	0.1	<0.0	-	0.1	<0.0
LysoPC a C28:1	6	0	0.10	7	7	2	0.69	5	1	0.63	4	1	4	8	5	1.26	6	1	1.18	6	1	1.22	4	1

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 5. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 19. Serum concentrations of phosphatidylcholine diacyls[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Phophatidylcholine diacyls µmol/L	All SAM n=39 Mean±SD	Kwas n=21 Mean±SD	Mara n=18 Mean±SD	All SAM n=40 Mean±SD	Kwa n=21 Mean±SD	Mara n=19 Mean±SD	Stt (n=78) Mean±SD	nStt (n=79) Mean±SD
PC aa C24:0	0.23±0.10	0.22±0.10	0.25±0.09	0.24±0.08	0.22±0.06	0.26±0.10	0.19±0.06	0.19±0.06
PC aa C26:0	1.31±0.37	1.25±0.33	1.37±0.41	1.48±0.42	1.38±0.40	1.59±0.42	–	–
PC aa C28:1	2.01±1.16	1.51±0.78	2.59±1.28	2.24±1.09	1.82±0.92	2.71±1.08	1.61±1.06	2.08±1.46
PC aa C30:0	4.91±2.67	3.76±1.97	6.26±2.8	5.27±3.66	3.94±1.50	6.74±4.71	3.18±1.53	3.03±1.55
PC aa C30:2	0.22±0.27	0.18±0.26	0.28±0.28	0.29±0.41	0.42±0.51	0.14±0.19	0.44±0.19	0.42±0.17
PC aa C32:0	25.1±10.4	23.0±12.0	27.7±7.7	22.6±11.17	21.9±12.5	23.3±9.7	16.0±8.4	12.4±5.22
PC aa C32:1	20.0±15.5	20.5±14.7	19.4±16.9	25.4±16.8	23.9±16.7	27.1±17.3	10.8±7.0	7.51±4.58
PC aa C32:2	2.91±1.42	2.5±1.3	3.39±1.48	3.13±1.99	2.37±1.37	3.98±2.25	2.13±1.08	2.11±1.05
PC aa C32:3	0.27±0.08	0.25±0.08	0.28±0.08	0.31±0.13	0.30±0.10	0.31±0.15	0.24±0.06	0.25±0.06
PC aa C34:1	148±36	133±24	165±41	157±28	162±32	151±24	136±49	111±35
PC aa C34:2	168±38	151±23	188±43	177±37	184±35	170±40	213±51	186±39
PC aa C34:3	8.88±5.09	8.93±4.07	8.81±6.19	12.2±6.6	13.1±7.8	11.2±5.0	6.52±3.06	4.98±2.19
PC aa C34:4	0.62±0.31	0.52±0.24	0.73±0.34	0.69±0.44	0.56±0.27	0.84±0.55	1.03±0.67	1.12±0.53
PC aa C36:0	4.93±3.39	4.56±4.06	5.36±2.45	4.34±2.43	3.96±2.24	4.76±2.61	1.99±0.74	2.03±0.87
PC aa C36:1	49.4±23.6	47.7±18.5	51.3±28.9	66.7±31.1	70.4±32.0	62.6±30.5	31.2±12.1	26.8±7.6
PC aa C36:2	144±43	133±32	156±51	162±37	167±37	157±38	135±37	121±26
PC aa C36:3	60.1±25.4	53.2±22.3	68.1±27.0	92.3±35.0	98.0±38.5	86.1±30.4	68.1±20.1	64.2±15.0
PC aa C36:4	106±38	88.4±31.8	127±34	101±31	97.5±26.2	105±37	140±38	135±25
PC aa C36:5	4.73±2.89	3.9±2.2	5.71±3.37	5.08±2.90	4.70±2.51	5.50±3.30	6.78±2.65	6.34±2.50
PC aa C36:6	0.44±0.28	0.34±0.20	0.54±0.32	0.40±0.29	0.34±0.21	0.46±0.35	0.58±0.36	0.67±0.29
PC aa C38:0	3.44±1.49	2.97±1.09	3.98±1.74	3.23±1.14	3.07±0.96	3.41±1.31	2.49±0.82	2.46±0.82
PC aa C38:1	0.73±1.06	0.68±1	0.78±1.15	1.09±1.08	1.06±0.93	1.12±1.26	0.79±0.39	0.71±0.32
PC aa C38:3	21.3±8.5	19.0±6.4	24.0±9.91	34.0±18.1	32.5±19.8	35.7±16.3	34.9±10.2	35.5±8.0
PC aa C38:4	63.6±25.2	52.8±18.6	76.3±26.4	61.7±27.8	57.4±29.1	66.4±26.3	96.9±26.5	97.7±19.0
PC aa C38:5	20.6±10.9	16.9±7.6	24.8±12.7	21.3±8.4	20.5±7.7	22.3±9.2	33.2±10.3	32.8±7.2
PC aa C38:6	46.4±28.6	28.9±12.4	66.9±28.6	41.6±23.4	34.9±16.9	49.1±27.5	58.0±22.3	63.6±17.0
PC aa C40:1	0.51±0.19	0.47±0.18	0.56±0.20	0.52±0.17	0.49±0.16	0.55±0.19	–	–
PC aa C40:2	0.42±0.30	0.44±0.39	0.40±0.15	0.39±0.12	0.40±0.11	0.38±0.14	0.29±0.09	0.28±0.10
PC aa C40:3	0.42±0.20	0.44±0.24	0.40±0.14	0.48±0.27	0.44±0.21	0.52±0.33	0.52±0.15	0.50±0.14
PC aa C40:4	2.59±1.46	2.13±0.72	3.12±1.89	2.73±1.54	2.47±1.26	3.02±1.79	4.49±1.69	4.23±1.14
PC aa C40:5	5.11±2.83	4.45±2.75	5.88±2.8	5.71±3.4	5.36±3.07	6.09±3.78	9.80±3.42	9.81±2.60
PC aa C40:6	18.0±8.1	13.8±6.5	22.9±7.1	16.64±8.75	13.8±7.0	19.8±9.5	24.6±8.6	26.9±7.0
PC aa C42:0	0.55±0.23	0.50±0.19	0.62±0.27	0.51±0.18	0.47±0.16	0.55±0.19	0.67±0.19	0.66±0.20

PC aa C42:1	0.27±0.13	0.25±0.11	0.30±0.14	0.26±0.09	0.24±0.08	0.29±0.09	0.38±0.11	0.39±0.14
PC aa C42:2	0.20±0.08	0.19±0.09	0.22±0.07	0.21±0.08	0.20±0.07	0.21±0.09	0.23±0.08	0.22±0.08
PC aa C42:4	0.21±0.08	0.20±0.08	0.22±0.08	0.20±0.09	0.19±0.07	0.22±0.11	0.24±0.07	0.22±0.06
PC aa C42:5	0.26±0.10	0.23±0.07	0.29±0.12	0.30±0.14	0.27±0.10	0.33±0.17	0.41±0.12	0.40±0.11
PC aa C42:6	0.58±0.20	0.54±0.19	0.62±0.21	0.65±0.21	0.62±0.16	0.68±0.26	0.48±0.14	0.47±0.15

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 6. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 20. Group differences in serum concentrations of phosphatidylcholine diacyls1 assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Phophatidylcholine	SAM			Admission									Stabilization											
diacyls	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
µmol/L	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2	Est.	SEM	P2
PC aa C24:0	0.08	0.25	0.79	0.67	0.46	0.21	-0.56	0.18	<0.01	-0.57	0.18	<0.01	0.23	0.37	0.60	-0.62	0.17	<0.01	-0.65	0.17	<0.01	-0.64	0.16	<0.01
PC aa C26:0	0.41	0.19	0.07	0.47	0.33	0.23		–			–		0.46	0.34	0.25		–			–			–	
PC aa C28:1	0.20	0.14	0.20	0.87	0.26	<0.01	-0.17	0.16	0.35	-0.02	0.16	0.92	0.58	0.25	<0.05	-0.38	0.15	<0.05	-0.19	0.15	0.29	-0.28	0.14	0.07
PC aa C30:0	0.06	0.15	0.73	1.04	0.32	<0.01	-0.63	0.16	<0.01	-0.84	0.16	<0.01	0.75	0.33	<0.05	-0.72	0.15	<0.01	-0.93	0.15	<0.01	-0.83	0.14	<0.01
PC aa C30:2	0.18	0.30	0.61	0.56	0.38	0.21	-0.97	0.15	<0.01	-0.89	0.15	<0.01	-1.26	0.46	<0.05	-0.80	0.17	<0.01	-0.72	0.17	<0.01	-0.76	0.16	<0.01
PC aa C32:0	-0.29	0.14	0.09	0.64	0.29	0.05	-1.01	0.16	<0.01	-1.48	0.16	<0.01	0.23	0.32	0.56	-0.73	0.16	<0.01	-1.20	0.16	<0.01	-0.98	0.15	<0.01
PC aa C32:1	0.34	0.17	0.09	0.19	0.29	0.60	-0.86	0.15	<0.01	-1.24	0.15	<0.01	0.39	0.30	0.27	-1.20	0.15	<0.01	-1.59	0.15	<0.01	-1.40	0.14	<0.01
PC aa C32:2	0.02	0.22	0.95	0.68	0.35	0.09	-0.46	0.16	<0.05	-0.56	0.16	<0.01	0.96	0.42	0.05	-0.47	0.18	<0.05	-0.58	0.17	<0.01	-0.53	0.16	<0.01
PC aa C32:3	0.42	0.27	0.18	0.64	0.32	0.09	-0.29	0.16	0.12	-0.25	0.16	0.17	0.27	0.51	0.67	-0.72	0.19	<0.01	-0.68	0.19	<0.01	-0.70	0.17	<0.01
PC aa C34:1	0.22	0.15	0.21	0.67	0.23	<0.05	-0.41	0.19	<0.05	-0.96	0.18	<0.01	0.11	0.20	0.64	-0.65	0.18	<0.01	-1.18	0.18	<0.01	-0.92	0.17	<0.01
PC aa C34:2	0.22	0.20	0.35	0.80	0.27	<0.05	-0.99	0.19	<0.01	-0.44	0.19	<0.05	-0.36	0.30	0.31	-0.73	0.19	<0.01	-0.20	0.18	0.35	-0.46	0.17	<0.05
PC aa C34:3	-0.62	0.20	<0.01	0.29	0.28	0.38	-0.64	0.14	<0.01	-0.98	0.14	<0.01	-0.06	0.33	0.89	-1.23	0.15	<0.01	-1.59	0.14	<0.01	-1.41	0.13	<0.01
PC aa C34:4	0.12	0.15	0.53	0.62	0.22	<0.05	-0.93	0.17	<0.01	-1.06	0.17	<0.01	0.62	0.29	0.07	-0.82	0.17	<0.01	-0.94	0.17	<0.01	-0.88	0.16	<0.01
PC aa C36:0	-0.16	0.26	0.61	0.40	0.42	0.42	-1.27	0.15	<0.01	-1.29	0.15	<0.01	0.38	0.37	0.39	-1.12	0.14	<0.01	-1.13	0.14	<0.01	-1.13	0.13	<0.01
PC aa C36:1	0.60	0.17	<0.01	0.41	0.29	0.23	-0.92	0.14	<0.01	-1.12	0.13	<0.01	0.06	0.33	0.88	-1.52	0.14	<0.01	-1.72	0.14	<0.01	-1.62	0.13	<0.01
PC aa C36:2	0.51	0.20	<0.05	0.82	0.36	0.05	-0.25	0.19	0.26	-0.59	0.18	<0.01	-0.23	0.31	0.55	-0.74	0.18	<0.01	-1.10	0.17	<0.01	-0.93	0.16	<0.01
PC aa C36:3	1.21	0.26	<0.01	1.20	0.38	<0.01	-0.42	0.17	<0.05	-0.34	0.17	0.07	-0.25	0.42	0.62	-0.77	0.17	<0.01	-0.86	0.16	<0.01	-0.82	0.15	<0.01
PC aa C36:4	-0.12	0.22	0.66	1.28	0.37	<0.01	-0.99	0.17	<0.01	-0.90	0.17	<0.01	-0.13	0.36	0.77	-1.09	0.16	<0.01	-1.01	0.16	<0.01	-1.05	0.14	<0.01
PC aa C36:5	-0.18	0.22	0.51	1.25	0.33	<0.01	-0.84	0.17	<0.01	-0.76	0.17	<0.01	-0.49	0.37	0.26	-0.67	0.17	<0.01	-0.58	0.17	<0.01	-0.62	0.15	<0.01
PC aa C36:6	-0.17	0.21	0.49	0.87	0.29	<0.05	-0.59	0.17	<0.01	-0.84	0.17	<0.01	-0.33	0.28	0.32	-0.78	0.17	<0.01	-1.01	0.17	<0.01	-0.90	0.15	<0.01
PC aa C38:0	-0.10	0.20	0.67	0.78	0.42	0.11	-0.77	0.18	<0.01	-0.81	0.18	<0.01	-0.39	0.33	0.32	-0.68	0.17	<0.01	-0.71	0.17	<0.01	-0.70	0.15	<0.01
PC aa C38:1	0.59	0.26	0.06	0.04	0.52	0.95	-0.42	0.17	<0.05	-0.32	0.16	0.09	-0.10	0.51	0.88	-0.19	0.17	0.35	-0.28	0.17	0.14	-0.24	0.15	0.18
PC aa C38:3	1.06	0.22	<0.01	0.86	0.29	<0.05	-1.30	0.15	<0.01	-1.41	0.15	<0.01	-0.49	0.44	0.35	-0.24	0.17	0.21	-0.34	0.16	0.06	-0.29	0.15	0.08

PC aa C38:4	-0.14	0.20	0.56	1.05	0.31	<0.01	1.16	0.14	<0.01	1.23	0.14	<0.01	0.48	0.39	0.29	1.28	0.15	<0.01	1.36	0.15	<0.01	1.32	0.13	<0.01
PC aa C38:5	0.19	0.20	0.42	1.05	0.39	<0.05	1.28	0.15	<0.01	1.33	0.15	<0.01	0.17	0.34	0.68	1.09	0.14	<0.01	1.13	0.14	<0.01	1.11	0.13	<0.01
PC aa C38:6	-0.17	0.19	0.47	1.64	0.31	<0.01	0.79	0.16	<0.01	0.98	0.16	<0.01	0.49	0.37	0.27	0.95	0.15	<0.01	1.15	0.15	<0.01	1.05	0.14	<0.01
PC aa C40:1	0.04	0.22	0.88	0.47	0.36	0.27	–			–			0.26	0.33	0.51	–			–			–		
PC aa C40:2	-0.08	0.28	0.82	-0.33	0.55	0.62	-0.83	0.19	<0.01	-0.91	0.18	<0.01	-0.10	0.30	0.80	-0.78	0.14	<0.01	-0.84	0.14	<0.01	-0.81	0.13	<0.01
PC aa C40:3	0.27	0.25	0.35	-0.33	0.40	0.49	0.57	0.17	<0.01	0.48	0.17	<0.05	0.35	0.47	0.53	0.25	0.18	0.23	0.16	0.18	0.46	0.21	0.17	0.29
PC aa C40:4	0.09	0.17	0.68	0.78	0.32	<0.05	1.22	0.15	<0.01	1.17	0.15	<0.01	0.46	0.33	0.24	1.11	0.15	<0.01	1.06	0.15	<0.01	1.08	0.14	<0.01
PC aa C40:5	0.16	0.19	0.49	0.67	0.32	0.07	1.39	0.14	<0.01	1.44	0.14	<0.01	0.08	0.35	0.86	1.22	0.14	<0.01	1.26	0.14	<0.01	1.24	0.13	<0.01
PC aa C40:6	-0.24	0.19	0.28	1.22	0.30	<0.01	0.85	0.15	<0.01	1.09	0.15	<0.01	0.71	0.37	0.10	1.09	0.16	<0.01	1.32	0.16	<0.01	1.21	0.14	<0.01
PC aa C42:0	-0.22	0.18	0.30	0.52	0.39	0.26	0.58	0.19	<0.01	0.56	0.19	<0.01	0.32	0.31	0.39	0.78	0.18	<0.01	0.76	0.18	<0.01	0.77	0.16	<0.01
PC aa C42:1	-0.08	0.16	0.69	0.26	0.32	0.50	0.82	0.19	<0.01	0.91	0.18	<0.01	0.40	0.25	0.16	0.86	0.17	<0.01	0.97	0.17	<0.01	0.92	0.16	<0.01
PC aa C42:2	0.02	0.22	0.94	0.43	0.35	0.30	0.22	0.19	0.31	0.16	0.19	0.49	-0.01	0.35	0.99	0.20	0.19	0.38	0.12	0.19	0.58	0.16	0.17	0.43
PC aa C42:4	-0.09	0.23	0.74	0.32	0.39	0.49	0.37	0.18	0.07	0.23	0.18	0.27	0.47	0.43	0.36	0.43	0.19	<0.05	0.28	0.19	0.18	0.35	0.17	0.06
PC aa C42:5	0.31	0.18	0.13	0.56	0.26	0.06	1.17	0.16	<0.01	1.11	0.16	<0.01	0.53	0.35	0.19	0.84	0.17	<0.01	0.77	0.17	<0.01	0.81	0.16	<0.01
PC aa C42:6	-0.38	0.23	0.16	0.46	0.37	0.29	-0.62	0.17	<0.01	-0.62	0.16	<0.01	-0.34	0.36	0.44	-1.03	0.16	<0.01	-1.02	0.16	<0.01	-1.03	0.15	<0.01

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 6. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 21. Serum concentrations of phosphatidylcholine acyl-alkyls[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Phophatidylcholine acyl-alkyls µmol/L	All SAM n=39 Mean±SD	Kwas n=21 Mean±SD	Mara n=18 Mean±SD	All SAM n=40 Mean±SD	Kwa n=21 Mean±SD	Mara n=19 Mean±SD	Stt (n=78) Mean±SD	nStt (n=79) Mean±SD
PC ae C30:0	0.61±0.28	0.5±0.23	0.73±0.30	0.61±0.26	0.51±0.14	0.72±0.31	–	–
PC ae C30:1	0.33±0.21	0.26±0.14	0.41±0.25	0.35±0.2	0.33±0.22	0.37±0.18	0.21±0.08	0.19±0.10
PC ae C30:2	0.11±0.04	0.10±0.04	0.12±0.04	0.11±0.04	0.10±0.03	0.12±0.04	0.06±0.02	0.06±0.02
PC ae C32:1	3.53±1.20	3.35±0.92	3.75±1.47	3.31±1.49	3.09±1.19	3.55±1.77	2.50±0.93	2.21±0.70
PC ae C32:2	0.60±0.21	0.60±0.24	0.59±0.17	0.51±0.21	0.54±0.25	0.47±0.16	0.45±0.12	0.42±0.11
PC ae C34:0	1.44±0.55	1.35±0.62	1.55±0.44	1.41±0.63	1.26±0.63	1.57±0.61	0.99±0.41	0.81±0.28
PC ae C34:1	8.89±3.37	8.43±3.59	9.43±3.10	8.50±3.28	8.39±3.01	8.62±3.64	6.74±2.95	5.28±1.87
PC ae C34:2	6.89±2.36	6.6±2.4	7.22±2.35	6.53±2.44	6.54±2.60	6.53±2.31	5.56±1.66	4.81±1.13
PC ae C34:3	5.19±2.01	5.66±2.06	4.64±1.85	3.96±1.64	4.09±1.80	3.80±1.46	4.26±1.55	4.29±1.08
PC ae C36:0	3.12±1.49	2.82±1.27	3.47±1.68	4.05±1.8	3.86±1.64	4.26±1.99	0.60±0.18	0.56±0.13
PC ae C36:1	7.84±2.97	7.17±2.59	8.61±3.27	7.67±2.32	7.79±2.28	7.55±2.43	4.06±1.72	3.38±1.34
PC ae C36:2	8.72±3.07	8.13±2.93	9.41±3.17	8.34±2.89	8.52±2.72	8.15±3.13	6.75±2.56	5.58±1.92
PC ae C36:3	4.36±1.61	4.17±1.53	4.58±1.72	4.67±1.58	4.65±1.74	4.68±1.43	3.66±1.08	3.35±0.78
PC ae C36:4	13.0±4.76	10.8±3.8	15.5±4.6	12.2±6.3	10.6±4.80	13.9±7.3	13.7±4.93	12.8±3.7
PC ae C36:5	9.80±3.89	8.9±3.3	10.8±4.3	7.66±3.50	7.36±3.97	7.98±2.97	10.9±4.7	11.7±3.8
PC ae C38:0	1.41±0.73	1.17±0.63	1.7±0.76	1.77±0.88	1.74±0.93	1.79±0.84	1.03±0.31	1.09±0.31
PC ae C38:1	1.94±1.07	1.81±1.14	2.1±1.0	2.35±1.07	2.34±0.78	2.37±1.34	0.39±0.18	0.35±0.17
PC ae C38:2	1.78±0.85	1.88±0.87	1.67±0.83	1.87±0.75	1.77±0.69	1.99±0.81	1.40±0.48	1.21±0.46
PC ae C38:3	2.08±0.82	1.84±0.65	2.36±0.92	2.16±0.73	2.17±0.77	2.15±0.70	2.18±0.72	2.02±0.60
PC ae C38:4	8.96±3.38	7.69±2.88	10.5±3.38	8.26±3.89	7.18±3.24	9.47±4.26	10.1±2.6	9.49±2.33
PC ae C38:5	13.2±4.8	11.8±4.4	14.8±4.8	12.1±5.4	11.4±5.70	12.8±5.0	14.4±4.23	13.6±3.3
PC ae C38:6	5.01±2.02	4.17±1.77	5.98±1.90	4.42±2.20	4.11±1.52	4.77±2.78	5.18±2.01	5.32±1.63
PC ae C40:1	0.63±0.30	0.57±0.28	0.70±0.32	0.66±0.29	0.58±0.27	0.75±0.30	0.70±0.23	0.73±0.24
PC ae C40:2	0.82±0.38	0.71±0.33	0.95±0.40	0.82±0.27	0.79±0.28	0.85±0.26	0.68±0.20	0.69±0.28
PC ae C40:3	0.77±0.33	0.70±0.33	0.85±0.33	0.80±0.29	0.77±0.34	0.82±0.23	0.62±0.15	0.61±0.16
PC ae C40:4	1.65±0.61	1.43±0.43	1.91±0.69	1.55±0.48	1.42±0.41	1.69±0.54	1.86±0.47	1.79±0.47
PC ae C40:5	2.68±1.08	2.38±0.95	3.04±1.13	2.36±0.69	2.26±0.67	2.46±0.72	2.55±0.64	2.42±0.63
PC ae C40:6	3.24±1.51	2.55±0.84	4.03±1.73	2.90±1.19	2.56±0.93	3.27±1.35	3.57±0.98	3.63±1.04
PC ae C42:1	0.38±0.19	0.36±0.23	0.41±0.13	0.39±0.15	0.35±0.14	0.44±0.15	0.58±0.16	0.54±0.17
PC ae C42:2	0.29±0.16	0.27±0.15	0.32±0.16	0.29±0.10	0.28±0.09	0.30±0.11	0.39±0.13	0.39±0.17
PC ae C42:3	0.35±0.15	0.31±0.12	0.39±0.17	0.38±0.11	0.35±0.10	0.42±0.12	0.46±0.13	0.47±0.15
PC ae C42:4	0.56±0.21	0.51±0.18	0.61±0.22	0.57±0.19	0.57±0.18	0.58±0.21	0.63±0.19	0.62±0.16

PC ae C42:5	1.4±0.5	1.30±0.48	1.52±0.51	1.39±0.42	1.26±0.38	1.53±0.43	1.57±0.39	1.55±0.34
PC ae C44:3	0.12±0.05	0.11±0.05	0.13±0.04	0.12±0.04	0.12±0.04	0.12±0.04	0.26±0.06	0.26±0.06
PC ae C44:4	0.23±0.08	0.22±0.07	0.26±0.08	0.24±0.08	0.23±0.08	0.25±0.07	0.31±0.07	0.31±0.06
PC ae C44:5	0.72±0.28	0.67±0.31	0.78±0.24	0.81±0.27	0.73±0.23	0.89±0.29	1.16±0.36	1.15±0.32
PC ae C44:6	1.0±0.39	0.91±0.34	1.11±0.42	0.98±0.34	0.92±0.35	1.05±0.32	1.69±0.45	1.69±0.43

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 7. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 22. Group differences in serum concentrations of phosphatidylcholine acyl-alkyls[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Phophatidylcholine	SAM			Admission									Stabilization											
acyl-alkyls	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
µmol/L	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]
PC ae C30:0	0.01	0.16	0.97	0.84	0.35	<0.05		–			–		0.58	0.29	0.08		–			–			–	
PC ae C30:1	0.12	0.26	0.70	0.80	0.41	0.09	-0.70	0.16	<0.01	-0.84	0.16	<0.01	0.12	0.44	0.83	-0.83	0.16	<0.01	-0.96	0.16	<0.01	-0.89	0.14	<0.01
PC ae C30:2	0.13	0.22	0.62	0.75	0.41	0.11	-1.24	0.15	<0.01	-1.22	0.14	<0.01	0.63	0.35	0.12	-1.36	0.14	<0.01	-1.36	0.13	<0.01	-1.36	0.12	<0.01
PC ae C32:1	-0.26	0.20	0.27	0.35	0.32	0.35	-0.90	0.16	<0.01	-1.20	0.16	<0.01	0.28	0.40	0.56	-0.63	0.17	<0.01	-0.94	0.17	<0.01	-0.79	0.16	<0.01
PC ae C32:2	-0.56	0.21	<0.05	0.34	0.39	0.47	-0.96	0.17	<0.01	-1.08	0.16	<0.01	-0.25	0.44	0.63	-0.38	0.17	<0.05	-0.52	0.17	<0.01	-0.45	0.15	<0.01
PC ae C34:0	-0.12	0.16	0.53	0.56	0.31	0.12	-0.90	0.16	<0.01	-1.29	0.16	<0.01	0.89	0.37	<0.05	-0.81	0.17	<0.01	-1.19	0.16	<0.01	-1.01	0.15	<0.01
PC ae C34:1	-0.11	0.18	0.62	0.62	0.31	0.08	-0.77	0.17	<0.01	-1.25	0.17	<0.01	0.21	0.31	0.57	-0.66	0.17	<0.01	-1.14	0.16	<0.01	-0.91	0.16	<0.01
PC ae C34:2	-0.18	0.24	0.55	0.57	0.36	0.18	-0.65	0.17	<0.01	-1.05	0.17	<0.01	0.18	0.39	0.71	-0.47	0.17	<0.05	-0.87	0.17	<0.01	-0.68	0.16	<0.01
PC ae C34:3	-0.82	0.22	<0.01	-0.49	0.38	0.28	-0.59	0.19	<0.01	-0.47	0.18	<0.05	-0.14	0.41	0.79	-0.24	0.19	0.27	-0.34	0.18	0.10	-0.29	0.17	0.13
PC ae C36:0	0.42	0.13	<0.01	0.33	0.25	0.27	-1.68	0.07	<0.01	-1.73	0.07	<0.01	-0.23	0.20	0.34	-2.10	0.06	<0.01	-2.14	0.06	<0.01	-2.12	0.06	<0.01
PC ae C36:1	0.00	0.16	0.99	0.42	0.27	0.19	-1.38	0.14	<0.01	-1.66	0.14	<0.01	-0.06	0.22	0.83	-1.39	0.13	<0.01	-1.66	0.13	<0.01	-1.53	0.12	<0.01
PC ae C36:2	-0.12	0.20	0.62	0.73	0.29	<0.05	-0.80	0.17	<0.01	-1.19	0.17	<0.01	-0.08	0.33	0.86	-0.67	0.17	<0.01	-1.08	0.17	<0.01	-0.88	0.16	<0.01
PC ae C36:3	0.24	0.22	0.36	0.69	0.36	0.10	-0.52	0.17	<0.01	-0.74	0.17	<0.01	-0.32	0.38	0.49	-0.76	0.17	<0.01	-0.98	0.17	<0.01	-0.88	0.16	<0.01
PC ae C36:4	-0.30	0.22	0.25	1.12	0.33	<0.01	-0.27	0.17	0.17	-0.07	0.17	0.75	-0.72	0.43	0.15	-0.57	0.18	<0.01	-0.37	0.18	0.07	-0.46	0.17	<0.05
PC ae C36:5	-0.64	0.19	<0.01	0.57	0.35	0.17	-0.41	0.17	<0.05	-0.53	0.16	<0.01	-0.29	0.36	0.50	-1.05	0.16	<0.01	-1.18	0.16	<0.01	-1.11	0.15	<0.01
PC ae C38:0	0.58	0.27	0.06	1.08	0.41	<0.05	-0.64	0.16	<0.01	-0.50	0.16	<0.01	-0.39	0.44	0.47	-1.24	0.16	<0.01	-1.10	0.16	<0.01	-1.17	0.14	<0.01
PC ae C38:1	0.34	0.18	0.10	0.30	0.30	0.39	-1.61	0.09	<0.01	-1.68	0.09	<0.01	-0.02	0.25	0.95	-1.96	0.08	<0.01	-2.02	0.08	<0.01	-1.99	0.07	<0.01
PC ae C38:2	0.17	0.23	0.55	-0.05	0.40	0.92	-0.62	0.17	<0.01	-0.90	0.17	<0.01	-0.37	0.36	0.39	-0.77	0.16	<0.01	-1.07	0.16	<0.01	-0.92	0.15	<0.01
PC ae C38:3	0.15	0.25	0.62	0.84	0.40	0.07	-0.14	0.19	0.54	-0.05	0.19	0.85	-0.08	0.37	0.86	-0.02	0.19	0.93	-0.21	0.18	0.34	-0.12	0.17	0.56
PC ae C38:4	-0.35	0.23	0.20	1.03	0.38	<0.05	-0.50	0.17	<0.01	-0.30	0.17	0.11	-0.75	0.46	0.17	-0.85	0.18	<0.01	-0.64	0.18	<0.01	-0.75	0.16	<0.01
PC ae C38:5	-0.32	0.25	0.28	0.88	0.40	0.06	-0.42	0.18	<0.05	-0.24	0.17	0.23	-0.44	0.44	0.39	-0.75	0.18	<0.01	-0.57	0.18	<0.01	-0.66	0.16	<0.01
PC ae C38:6	-0.35	0.21	0.17	1.12	0.37	<0.01	-0.24	0.18	0.26	-0.28	0.18	0.17	-0.26	0.38	0.58	-0.58	0.18	<0.01	-0.63	0.18	<0.01	-0.61	0.16	<0.01

PC ae C40:1	0.12	0.23	0.67	0.55	0.41	0.25	-0.30	0.19	0.17	-0.42	0.19	<0.05	0.68	0.38	0.13	-0.17	0.19	0.43	-0.29	0.19	0.17	-0.23	0.17	0.23
PC ae C40:2	0.05	0.22	0.87	0.95	0.44	0.06	-0.47	0.19	<0.05	-0.46	0.19	<0.05	0.42	0.34	0.30	-0.54	0.18	<0.01	-0.52	0.17	<0.01	-0.53	0.16	<0.01
PC ae C40:3	0.16	0.26	0.62	0.78	0.48	0.16	-0.62	0.18	<0.01	-0.66	0.18	<0.01	0.32	0.41	0.51	-0.78	0.16	<0.01	-0.83	0.16	<0.01	-0.81	0.15	<0.01
PC ae C40:4	-0.20	0.22	0.44	0.80	0.40	0.09	-0.52	0.19	<0.05	-0.36	0.19	0.09	0.50	0.36	0.24	-0.69	0.18	<0.01	-0.54	0.18	<0.01	-0.61	0.16	<0.01
PC ae C40:5	-0.39	0.24	0.15	0.96	0.46	0.07	-0.08	0.19	0.73	-0.27	0.19	0.23	0.25	0.36	0.57	-0.31	0.18	0.13	-0.12	0.18	0.56	-0.21	0.16	0.26
PC ae C40:6	-0.29	0.21	0.25	1.37	0.39	<0.01	-0.46	0.18	<0.05	-0.48	0.18	<0.05	-0.55	0.37	0.20	-0.75	0.17	<0.01	-0.76	0.17	<0.01	-0.75	0.16	<0.01
PC ae C42:1	0.05	0.17	0.82	0.39	0.34	0.33	-1.04	0.17	<0.01	-0.87	0.17	<0.01	-0.52	0.29	0.13	-0.97	0.16	<0.01	-0.80	0.16	<0.01	-0.89	0.15	<0.01
PC ae C42:2	0.03	0.16	0.89	0.50	0.37	0.25	-0.65	0.19	<0.01	-0.69	0.19	<0.01	-0.26	0.25	0.36	-0.60	0.18	<0.01	-0.64	0.18	<0.01	-0.62	0.16	<0.01
PC ae C42:3	0.29	0.20	0.21	0.72	0.36	0.09	-0.80	0.19	<0.01	-0.90	0.19	<0.01	-0.50	0.27	0.11	-0.51	0.18	<0.05	-0.61	0.18	<0.01	-0.56	0.16	<0.01
PC ae C42:4	0.10	0.25	0.76	0.57	0.38	0.20	-0.47	0.19	<0.05	-0.36	0.19	0.10	-0.04	0.38	0.93	-0.37	0.19	0.08	-0.26	0.19	0.22	-0.32	0.17	0.10
PC ae C42:5	-0.03	0.24	0.93	0.51	0.43	0.32	-0.53	0.19	<0.01	-0.46	0.19	<0.05	-0.72	0.37	0.09	-0.54	0.18	<0.01	-0.47	0.18	<0.05	-0.51	0.16	<0.01
PC ae C44:3	0.02	0.10	0.89	0.23	0.20	0.32	-1.73	0.13	<0.01	-1.63	0.13	<0.01	-0.03	0.17	0.89	-1.70	0.12	<0.01	-1.61	0.12	<0.01	-1.65	0.11	<0.01
PC ae C44:4	0.11	0.21	0.67	0.59	0.35	0.15	-1.01	0.17	<0.01	-0.97	0.17	<0.01	-0.43	0.35	0.31	-0.89	0.17	<0.01	-0.86	0.17	<0.01	-0.87	0.16	<0.01
PC ae C44:5	0.26	0.18	0.21	0.43	0.29	0.21	-1.28	0.17	<0.01	-1.25	0.16	<0.01	-0.34	0.27	0.28	-1.03	0.16	<0.01	-0.99	0.16	<0.01	-1.01	0.15	<0.01
PC ae C44:6	-0.05	0.17	0.82	0.44	0.27	0.17	-1.38	0.15	<0.01	-1.38	0.14	<0.01	-0.17	0.26	0.59	-1.42	0.14	<0.01	-1.42	0.14	<0.01	-1.42	0.13	<0.01

[1] The estimates, SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 7. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 23. Serum concentrations of electrolytes and other markers[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Other Markers	All SAM	Kwas	Mara	All SAM	Kwa	Mara	Stt	nStt
	n=39	n=21	n=18	n=40	n=21	n=19	(n=78)	(n=79)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Albumin, g/L	24.8±8.1	20.3±6.1	30.1±6.8	27.9±8.6	24.19±8.07	32.1±7.2	–	–
Magnesium, µmol/L	0.84±0.14	0.80±0.09	0.89±0.17	0.86±0.15	0.87±0.13	0.84±0.17	–	–
Phosphate, µmol/L	1.25±0.38	1.22±0.33	1.28±0.44	1.60±0.36	1.50±0.29	1.71±0.40	–	–
Potassium, µmol/L	4.26±1.19	4.38±1.02	4.12±1.38	5.95±1.56	5.83±1.13	6.09±1.97	–	–
Sodium, µmol/L	137±6	137.7±4.3	135±7	136±7	138±9	132±4	–	–
Sugars, µmol/L	6130±2160	6560±1980	5630±2300	4950±2100	4760±1500	5160±2640	–	–

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 8. Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 24. Group differences in serum concentrations of electrolytes and other markers[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Other Markers	SAM			Admission									Stabilization											
	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]	Est.	SEM	P[2]
Albumin, g/L	0.36	0.05	<0.01	1.04	0.26	<0.01	–			–			0.66	0.29	<0.05	–			–			–		
Magnesium, µmol/L	0.10	0.22	0.72	0.56	0.30	0.11	–			–			-0.65	0.34	0.10	–			–			–		
Phosphate, µmol/L	0.86	0.18	<0.01	0.18	0.34	0.66	–			–			0.28	0.26	0.37	–			–			–		
Potassium, µmol/L	1.12	0.17	<0.01	-0.08	0.30	0.83	–			–			0.24	0.27	0.46	–			–			–		
Sodium, µmol/L	-0.17	0.21	0.51	-0.34	0.30	0.34	–			–			-0.86	0.37	<0.05	–			–			–		
Sugars, µmol/L	-0.64	0.22	<0.01	-0.60	0.32	0.11	–			–			0.06	0.33	0.89	–			–			–		

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 8. Adm, admission; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 25. Serum concentrations of summary values and ratios of metabolites[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

	SAM at admission			SAM at stabilization			Community Controls	
Summary values and ratios	All SAM n=39 Mean±SD	Kwas n=21 Mean±SD	Mara n=18 Mean±SD	All SAM n=40 Mean±SD	Kwa n=21 Mean±SD	Mara n=19 Mean±SD	Stt (n=78) Mean±SD	nStt (n=79) Mean±SD
BCAAs	161±63.4	148±51	176±74	338±157	360±177	315±133	348±96	391±107
C2/C0	0.43±0.44	0.27±0.18	0.61±0.57	0.42±0.43	0.46±0.51	0.37±0.34	0.22±0.13	0.23±0.13
Essential amino acids	458±133	405±93	521±148	747±292	749±322	744±264	744±197	847±208
Kynurenine-to-tryptophan	0.20±0.11	0.20±0.13	0.21±0.08	0.19±0.09	0.19±0.08	0.19±0.09	0.09±0.06	0.07±0.04
Serotonin-to-tryptophan	0.14±0.19	0.18±0.23	0.09±0.1	0.06±0.05	0.06±0.05	0.05±0.05	0.05±0.04	0.04±0.03
Total amino acids	2000±740	1750±590	2280±820	3190±1160	324±130	312±999	3220±680	3550±640

[1] Data are presented as mean ± SDs. [2] Metabolites ordered alphabetically. [3] Metabolite abbreviations are detailed in Supplementary Table 8. BCAAs, branched chain amino acids; C2/C0, ratio of acetylcarnitine on carnitine; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stt, Stunted.

Supplemental Table 26. Group differences in serum concentrations of summary values and ratios of metabolites[1] assessed in children hospitalized for severe acute malnutrition that were diagnosed with either kwashiorkor or marasmus and in children living in the community which were either stunted or non-stunted.

Summary values and ratios	SAM			Admission									Stabilization											
	Adm vs Stab			Kwa vs Mara			SAM vs Stt			SAM vs nStt			Kwa vs Mara			SAM vs Stt			SAM vs nStt			SAM vs Controls		
	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]	Est.	SE M	P[2]
BCAAs	1.48	0.19	<0.001	0.27	0.25	0.35	1.79	0.12	<0.001	2.01	0.12	<0.001	-0.04	0.40	0.93	0.28	0.14	0.07	0.53	0.14	0.01	0.41	0.13	0.01
C2/C0	-0.04	0.32	0.92	0.96	0.46	0.07	0.64	0.16	<0.001	0.68	0.16	<0.001	0.47	0.50	0.43	0.62	0.16	<0.001	0.64	0.16	<0.001	0.63	0.14	<0.001
Essential amino acids	1.25	0.21	<0.001	0.64	0.23	0.05	1.46	0.13	<0.001	1.78	0.13	<0.001	0.32	0.40	0.50	0.19	0.16	0.31	0.53	0.16	0.01	0.36	0.15	0.05
Kynurenine-to-tryptophan	-0.09	0.20	0.70	0.03	0.40	0.95	1.24	0.15	<0.001	1.51	0.14	<0.001	0.13	0.33	0.74	1.16	0.13	<0.001	1.41	0.13	<0.001	1.29	0.12	<0.001
Serotonin-to-tryptophan	-0.95	0.26	<0.001	1.35	0.55	0.07	1.04	0.19	<0.001	1.10	0.19	<0.001	0.24	0.26	0.63	0.12	0.20	0.28	0.17	0.20	0.12	0.15	0.09	0.15
Total amino acids	1.31	0.21	<0.001	0.66	0.25	0.08	1.58	0.13	<0.001	1.81	0.13	<0.001	0.18	0.41	0.73	0.23	0.16	0.16	0.49	0.16	0.01	0.37	0.15	0.05

[1] The estimates (Est.), SEMs and p-values for each comparison were obtained with linear or mixed linear models to account for repeated measures when testing for differences between patients at admission and prior-to-discharge. [2] Presented p-values are corrected with Benjamini & Hochberg False Discovery Rate (FDR) and the significance threshold was considered to be FDR-corrected p-values <0.05. [3] Metabolites ordered alphabetically. [4] Metabolite abbreviations are detailed in Supplementary Table 8. Adm, admission; BCAAs, branched chain amino acids; C2/C0, ratio of acetylcarnitine on carnitine; Kwa, kwashiorkor; Mara, marasmus; nStt, non-stunted; SAM, severe acute malnutrition; Stab, stabilization; Stt, stunted.

Supplemental Table 27. PLS-based feature selection of top-10 metabolites and other markers that differentiate between groups of children with kwashiorkor and marasmus at hospital admission for SAM.

	Metabolites[2]	Feature Stability (%)[1]	VIP score[3]
1	PC aa C38:6	100%	2.4
2	PC aa C40:6	100%	2
3	PC aa C36:4	100%	1.8
4	Threonine	90%	1.9
5	Kynurenine	90%	1.8
6	PC aa C34:2	90%	1.8
7	Tryptophan	90%	1.8
8	PC aa C34:1	90%	1.8
9	Albumin	80%	1.9
10	PC aa C38:4	60%	1.7
11	PC ae C40:6	40%	1.7
12	PC aa C36:5	30%	1.6
13	PC aa C40:4	20%	1.5
14	Aspartate	10%	1.5
15	PC ae C42:1	10%	1

[1] Feature stability indicates the percent of times that a metabolite is selected as a top-10 feature using sparse PLS-DA with 10-fold cross-validation. [2] Metabolites 1-9 are selected as being in the top 10 at least 80% of the time. [3] Variable Important for Projection (VIP) score is a metric that indicated the importance of the variable for the projection, variable with VIP scores ⩾ than 1 are accepted as significant for PLS projection.