**Materials**

All solvents and reagents used in the study were of analytical or HPLC grade quality. Acetonitrile (ACN), methanol (MeOH), chloroform (CHCl3), isopropanol (IPA) were purchased from Carlo Erba Reactifs (SDS, Peypin, France). Acetic acid, ammonia, and ammonium acetate were sourced from Sigma-Aldrich (Saint Quentin Fallavier, France). Water was deionized and purified using an ultra-pure water system (Milli-Q®, Millipore Corporation, Billerica, Massachusetts, USA). MSCAL6 ProteoMass LTQ/FT-Hybrid®, standard mixtures used for calibration of the MS instrument (positive and negative ionization mode) were obtained from Sigma-Aldrich (Saint Quentin Fallavier, France). Internal lipid standards covering glycerophospholipids [LysoPC, phosphatidylcholine (PC) and phosphatidylethanolamine (PE)], glycerolipid (triglyceride, TG), sphingolipid (ceramide, Cer) and fatty acids (FA) categories were purchased from Avanti Polar Lipids (Alabaster, Alabama, USA); namely, Lyso PC (15:0), PC (15:0/15:0), PE (17:0/17:0), TG (17:0/17:0/17:0), Cer (d18:1/17:0), FA C15:0 and C23:0 and prepared according to Gallart-Ayala et al.(1).

**Weight and head circumference** **Z-score determination**

To assess growth, body weight measurements were performed weekly from birth to discharge, using an electronic scale accurate to the nearest 0·1 g. Weight Z-score was calculated using the Lambda Mu Sigma (LMS) method. LMS method provides a way of obtaining smoothed growth percentile curves (3rd to 97th) where data were normalized by calculating for each series of age groups and the trend summarized by a smooth (L) curve and trends in the mean (M) and coefficient of variation (S) similarly smoothed (2). The resulting L, M and S curves contain the information to draw any centile curve, and to convert measurements (even extreme values) into exact SD scores. We used reference growth curves for which LMS parameters have been published for weight, height and head circumference. For birth and discharge (up to 41 weeks of postmenstrual age) measurements, Olsen’s preterm infant growth chart (3) was applied. Weight gain during hospitalization was assessed as the difference of weight Z-score (expressed in units of SD using the SD of the term category as the benchmark) between discharge and birth. Thereafter, infants were ranked, according to the change in weight Z-score between birth and hospital discharge. For the sake of feasibility, only 26 patients, ranked in the fast (F, n=11) and slow (S, n=15) postnatal growth, were enrolled in this sub-cohort study. These infants presented extreme values in change in weight Z-score between birth and hospital discharge (means: -1.54 and -0.48 SD for S and F group, respectively), and sufficient milk samplings from w2 to w7 of lactation were available for these infants. Head circumference was determined, weekly, with a non-stretch measuring tape, and the difference of head circumference Z-score between discharge and birth was calculated, as described above regarding weight.

**Milk sample preparation and analytical repeatability**.

Milk samples removed from -80°C storage were allowed to thaw on ice and prepared for LC-HRMS analysis. Modified liquid–liquid extraction method of Bligh-Dyer (4) was used to extract and separate water-soluble from lipophilic metabolites. Briefly, 200 µL of a methanol-chloroform (MeOH: CHCl3) mixture (1:1, v/v) and 50 µL of 150 mM sodium chloride were added to each aliquot of milk (50 µL) thawed on ice. Then, the liquid CHCl3 and H2O / MeOH phases were separated after centrifugation (10 000 g for 10 min). After two extractions with 100µL CHCl3, the organic layers were dried under a gentle nitrogen stream and subsequently reconstituted in 100 µL of acetonitrile-water (ACN: H2O 30:70, v/v) or acetonitrile-isopropanol-water (ACN: IPA: H2O 65:30:5, v/v/v) and 5 µL were injected the same day onto the LC–HRMS system. The methodologic precision associated with sample preparation and LC-HRMS measurement was determined on the basis of a quality control (QC) consisting of a pool of 10 mothers’ milk provided by the milk bank of Nantes Hospital Center. The QC was separated into aliquots stored at -20°C then, freshly extracted along with each sample batch and analyzed in a random order throughout the analytical run to evaluate potential bias of the measurements over the time.

**Milk total fatty acids analysis**

Total lipids were extracted as described above and 1ml of toluene was added to dissolve triglycerides in the dried organic phases. Total fatty acids were trans-esterified using trifluoride and the fatty acids methyl esters were extracted and analysed by gas chromatography using an Agilent Technologies 7890A® instrument (Perkin Elmer, France) as previously described in our lab ([5](#_ENREF_48)).

**Liquid Chromatography-High-Resolution-Mass Spectrometry (LC-HRMS) conditions and experiments**

A 1200 infinity series® high performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, California, USA) coupled to an Exactive Orbitrap® mass spectrometer (Thermo Fisher Scientific, Bremen, Germany) equipped with a heated electospray (H-ESI II) source (operating in polarity switch mode) was used for lipid profiling. The full instrument calibration was performed using a MSCAL6 ProteoMassT LTQ/FT-Hybrid ESI Pos/Neg® (Sigma–Aldrich). Xcalibur 2.2® (Thermo Fisher Scientific, San Jose, CA, USA) was used for data acquisition and analysis. Lipid species separation was performed on a reverse phase CSH® C18 (100 x 2.1 mm2 i.d., 1.7 µm particle size) column (Waters Corporation, Milford, MA) using ACN:H2O (60:40) and IPA:ACN:H2O (88:10:2) as solvent A and B, respectively; both containing 10 mM ammonium acetate and 0.1 % acetic acid according to Gallart-Ayala et al. (1). Then, a polarity switching ion mode (positive/negative) and ‘‘all ion fragmentation’’ (AIF) MS/MS mode (mass range m/z 100–2000) applying 50 eV in-source collision-induced dissociation (CID) fragmentation at a mass resolving power of 50,000 full width half maximum (FWHM) (m/z 200) and a scanning rate of 2 spectra were applied (1). External mass calibration without the use of specific lock masses was employed. A standard lipid solution was analyzed at the beginning and at the end of each batch of samples to control the accuracy and precision of the system (1). The robust quality assurance for each metabolic feature detected was assessed through the means ± SDs of the coefficient of variation (CV, %) for each [mz, retention time (RT)] features for 8 replicates of the QC per analysis sequence.

**Supplemental Material References**

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