**Supplementary Material**

**Exploring the Varied Clinical Presentation of Pediatric Asthma through the Metabolome**

Kevin M. Mendez, Priyadarshini Kachroo, Nicole Prince, Mengna Huang, Margaret Cote, Su H. Chu, Yulu Chen, Rinku Sharma, Julian Hecker, Liang Chen, Robert Gerszten, Clary Clish, Lydiana Avila, Juan C Celedón, Craig E. Wheelock, Scott T. Weiss, Michael McGeachie, David I. Broadhurst, Stacey N. Reinke, Rachel S. Kelly, Jessica A. Lasky-Su on behalf of the NHLBI Trans-Omics for Precision Medicine.

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**Supplementary Methods 1: Clinical Phenotyping of CAMP and GACRS**

Blood samples were collected after a fasting period, and the majority were processed within four hours; remaining samples are stored at the Channing laboratory. The same collection protocols were used for CAMP and for GACRS unless otherwise noted.

**Airway Hyperresponsiveness (AHR).** We used the same spirometry system for PFTs with Methacholine Challenge Testing to generate two AHR phenotypes. The methacholine was delivered by a DeVilbiss 646 nebulizer (Sunrise Medical, Carlsbad, CA) and a compressed air flow-meter. This setup delivers 0.13 ml of solution per minute. The nebulizer was attached to a 2-way Rudolph valve (Hans Rudolph Corp, Kansas City, MO). Children with FEV1 ≥65% of predicted on baseline spirometry underwent MCT, consisting of five breaths of saline solution followed by one breath of a 1 mg/ml methacholine solution, one and four breaths of a 5 mg/ml methacholine solution, and one breath of a 25 mg/ml methacholine solution. All inhalations lasted 6 seconds and followed by 2 seconds of breath holding. After each inhalation level, spirometry was done at 180, 210, and 240 s. The test was terminated before completion of the dosing schedule if the FEV1 declines by ≥20% from the best FEV1 after inhalation of saline solution. At the end of testing, each child received two puffs of albuterol, and spirometry as repeated after 15 minutes.

**Atopy.** Measurements of total serum IgE, allergy skin testing and atopic diagnoses were captured in the atopic domain to include six clinical atopy phenotypes (Table 1). Interviewers visited the households of participating children and asked them (if >12 years of age) and/or their parents and recorded their history/diagnosis of hay fever, eczema, allergies, and family history of asthma and allergic diseases. Ten common allergens were tested as per ISAAC protocol. Eight and four pricks were made with ALK lancets in the left and right forearms, respectively. The allergens tested were D. pteronyssinus, D. farina, B. germanica, P. americana, cat dander, dog dander, Alternaria tenuis, mixed grass pollen, mixed tree pollen, ragweed, and positive (histamine)/negative (diluent) controls. Serum total IgEs was determined by the UniCAP 250 system (Pharmacia & Upjohn, Kalamazoo, MI), with samples measured in duplicate.

**Lung Function.** Pulmonary Function Tests (PFTs) were used to assess lung function from which we generated ten lung function phenotypes (Table 1). Spirometry was done with an Eaglet Screener (ES) spirometer (Somerset Medical, Somerset, MA). All subjects were free of respiratory illnesses for ≥4 weeks. Tests were conducted with children seated and wearing a nose clip. Forced expiratory maneuvers were acceptable if they met or exceeded ATS criteria. As many as eight forced expiratory flow volume maneuvers were performed to obtain three acceptable measures. Baseline spirometry was followed by testing of bronchodilator response. After performing baseline spirometry, subjects were given 2 puffs of albuterol by an MDI with a spacer. After 15 minutes, each subject repeated the spirometric maneuvers.

**Th2 Inflammation.** Blood eosinophils counts per microliter were measured in children at the time of blood draw. Both a continuous measure and a dichotomized measure (EOS>300) were used as clinical phenotypes for Th2 inflammation.

**Non-Th2 Inflammation.** Blood neutrophil counts per microliter were measured in children in CAMP time of blood draw. Measures of neutrophil count and the percentage of neutrophil over the total blood cells count were used as clinical phenotypes for non-Th2 inflammation.

**Supplementary Methods 2: Metabolomic Profiling**

**LC-MS method descriptions**

**C8-pos:** Reversed-phase C8 chromatography/positive ion mode MS detection to measure lipids (Broad Institute). Analyses of polar and non-polar plasma lipids were conducted using an LC-MS system comprised of a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.) coupled to an Exactive Plus orbitrap mass spectrometer (Thermo Fisher Scientific). Plasma samples (10 μL) were extracted for lipid analyses using 190 μL of isopropanol containing 1,2-didodecanoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids) as an internal standard. After centrifugation, supernatants were injected directly onto a 100 x 2.1 mm, 1.7 μm ACQUITY BEH C8 column (Waters). The column was eluted isocratically with 80% mobile phase A (95:5:0.1 vol/vol/vol 10mM ammonium acetate/methanol/formic acid) for 1 minute followed by a linear gradient to 80% mobile- phase B (99.9:0.1 vol/vol methanol/formic acid) over 2 minutes, a linear gradient to 100% mobile phase B over 7 minutes, then 3 minutes at 100% mobile-phase B. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over 200–1100 m/z at 70,000 resolution and 3 Hz data acquisition rate. Other MS settings were: sheath gas 50, in source CID 5 eV, sweep gas 5, spray voltage 3 kV, capillary temperature 300°C, S-lens RF 60, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 100 ms. Raw data were processed using TraceFinder software (Thermo Fisher Scientific) for targeted peak integration and manual review of a subset of identified lipids and using Progenesis QI (Nonlinear Dynamics) for peak detection and integration of both lipids of known identify and unknowns. Lipid identities were determined based on comparison to reference plasma extracts and are denoted by total number of carbons in the lipid acyl chain(s) and total number of double bonds in the lipid acyl chain(s).

**C18-neg:** Reversed-phase C18 chromatography/negative ion mode MS detection to measure free fatty acids, bile acids, and metabolites of intermediate polarity (Broad Institute). Analyses of free fatty acids and bile acids were conducted using an LC-MS system comprised of a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.) coupled to a Q Exactive hybrid quadrupole orbitrap mass spectrometer (Thermo Fisher Scientific). Plasma samples (30 μL) were extracted using 90 uL of methanol containing 15R-15-methyl-PGA2, 15R-15-methyl-PGF2alpha, 15S-15-methyl-PGD2, 15S-15-methyl- PGE1, and 15S-15-methyl-PGE2 (Cayman Chemical Co.) internal standards and centrifuged (10 min, 9,000 x g, 4°C). The samples were injected onto a 150 x 2 mm ACQUITY BEH C18 column (Waters). The column was eluted isocratically at a flow rate of 400 μL/min with 60% mobile phase A (0.1% formic acid in water) for 4 minutes followed by a linear gradient to 100% mobile phase B (acetonitrile with 0.1% acetic acid) over 8 minutes. MS analyses were carried out in the negative ion mode using electrospray ionization, full scan MS acquisition over 200-550 m/z, and a resolution setting of 70,000. Other MS settings were: sheath gas 45, sweep gas 5, spray voltage - 3.5 kV, capillary temperature 320°C, S-lens RF 60, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 250 ms. Raw data were processed using TraceFinder software (Thermo Fisher Scientific) for targeted peak integration and manual review of a subset of identified metabolites and using Progenesis QI (Nonlinear Dynamics) for peak detection and integration of both metabolites of known identify and unknowns. Metabolite identities were confirmed using authentic reference standards.

**HILIC-pos:** Hydrophilic interaction liquid chromatography/positive ion mode MS detection to measure polar metabolites (Broad Institute). HILIC analyses of water soluble metabolites in the positive ionization mode were conducted using an LC-MS system comprised of a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.) coupled to a Q Exactive hybrid quadrupole orbitrap mass spectrometer (Thermo Fisher Scientific). Plasma samples (10 μL) were prepared via protein precipitation with the addition of nine volumes of 74.9:24.9:0.2 v/v/v acetonitrile/methanol/formic acid containing stable isotope-labeled internal standards (valine-d8, Sigma-Aldrich; St. Louis, MO; and phenylalanine-d8, Cambridge Isotope Laboratories; Andover, MA). The samples were centrifuged (10 min, 9,000 x g, 4°C), and the supernatants were injected directly onto a 150 x 2 mm, 3 μm Atlantis HILIC column (Waters). The column was eluted isocratically at a flow rate of 250 μL/min with 5% mobile phase A (10 mM ammonium formate and 0.1% formic acid in water) for 0.5 minute followed by a linear gradient to 40% mobile phase B (acetonitrile with 0.1% formic acid) over 10 minutes. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over 70-800 m/z at 70,000 resolution and 3 Hz data acquisition rate. Other MS settings were: sheath gas 40, sweep gas 2, spray voltage 3.5 kV, capillary temperature 350°C, S-lens RF 40, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 250 ms. Raw data were processed using TraceFinder software (Thermo Fisher Scientific) for targeted peak integration and manual review of a subset of identified metabolites and using Progenesis QI (Nonlinear Dynamics) for peak detection and integration of both metabolites of known identify and unknowns. Metabolite identities were confirmed using authentic reference standards.

**Amide-neg: Targeted negative ion mode analysis of central metabolites (BIDMC).**

Central metabolites including sugars, sugar phosphates, organic acids, purine, and pyrimidines, were extracted from 30 μL of plasma using acetonitrile and methanol and separated using a 100 x 2.1 mm XBridge Amide column (Waters). A high sensitivity Agilent 6490 QQQ MS (Agilent) was used to profile metabolites in the negative ion mode via multiple reaction monitoring (MRM) scanning. MRM parameters for approximately 200 metabolites were previously optimized by infusing authentic reference standards. Raw data were processed using MassHunter Quantitative Analysis Software (Agilent).

**QC prior to and during data acquisition.**

The analytical performance of the LC-MS systems and the quality of the metabolomics data were assured using several strategies. Before analyses of the study samples were initiated, reference plasma extracts and mixtures of synthetic reference standards containing up to ~150 metabolites each were analyzed to assure reproducibility of chromatographic retention times, quality of chromatographic peak shapes, and the sensitivity of the MS system. On a daily basis throughout the analytical run, internal standard signals were monitored in each sample to ensure that each injected properly and to monitor MS sensitivity. Generally, outliers (failed samples) were identified when internal standard levels were more than 2 standard deviations from the mean. Outlier samples were selected for reanalysis, using the same sample extract if the outlier was flagged within a day of its extraction, otherwise a fresh extract was prepared and analyzed. In addition, pairs of pooled reference samples (“PREFA” and “PREFB”) were inserted in the analysis queue at intervals of approximately 20 study samples for determination of reproducibility and data standardization. The pooled reference sample was created using small aliquots from each study sample at the time the samples are aliquoted for the four profiling methods. One pooled reference sample from each pair (either PREFA or PREFB) was used to standardize data across the run and between batches using “nearest-neighbor” scaling while a second pooled reference from each pair was used to calculate coefficients of variation (CVs) for every metabolite and unknown measured throughout the analysis. Metabolite signals in PREF samples were also evaluated daily to assure LC retention times and peak shapes. If the pooled reference sample data showed a loss of analytical performance, the queue was stopped until the problem was corrected and the analysis queue was restarted from the last point at which data quality was acceptable.

**Non targeted data processing**

Raw LC-MS data were acquired to the data acquisition computer interfaced to each LC- MS system and then stored on a robust and redundant file storage system (Isilon Systems) accessed via the Broad’s internal network. For data processing, the platform is equipped with >10 powerful workstations configured with multi-core XEON processors, >32 GB of RAM and 2 TB of fast storage (RAID 0 arrays of four drives or NVME ssd). Targeted data processing of known metabolites was achieved using TraceFinder software (Thermo Fisher Scientific). Identities of >600 plasma metabolites have been confirmed using authentic reference standards (MSI Level 1 ID(7)) and mixtures of reference standards and reference samples were included in each analysis queue to confirm IDs in every dataset. High resolution, nontargeted data were processed using Progenesis QI software (Nonlinear Dynamics) to detect peaks, perform chromatographic retention time alignment, and integrate peak areas. Metabolites of confirmed identity were then annotated in the dataset and unknowns are “tagged” using their measured mass to charge ratio (m/z) and retention time (RT). A significant challenge for large-scale, nontargeted metabolomics studies is accurate “alignment” on unknowns among batches of samples acquired over time. This challenge arises because of the large number of nontargeted features detected in every dataset and the occurrence of minor deviations in measured m/z and RT for each peak as a function of differences in instrument calibration and LC column performance over time. The Broad lab has developed an innovative feature alignment algorithm that overcomes this challenge. The software tool is deployed as a web app and uses a unique approach to detect landmark features and non-parametric retention time scaling to accurately match unknowns between datasets. The output from this workflow is a table of concatenated data from each of the methods, expressed as individual samples in columns and metabolite abundances in rows.

**Data Levels**

In this analysis only Broad defined level 3 quality data was used. i.e., data aggregated in features. That is, redundant ion features were filtered out of the non-targeted datasets. The electrospray ionization process used in LC-MS can generate multiple ion features from a single analyte. Though these methods are aimed at maximizing the relative abundance of [M+H]+ and [M-H]- ions, may also detect lower abundance ion adducts and source fragments. The Broad lab has developed a Python-based web app that can process tabularized “normalized data” and annotates clusters of highly correlated, co-eluting LC-MS peaks. This method computes Spearman correlation coefficients among all LC-MS peaks that coelute within 0.025 minutes of one another. “Cliques” of highly correlated features are then identified based on a Spearman coefficient threshold of 0.8. The algorithm determines whether an [M+H]+ ion (positive ion mode data) or an [M-H]- ion (negative ion mode data) can be identified using mass differences among ions in each clique and, if so, selects that feature as the major ion. Otherwise, the most abundant ion was is selected as the major ion. Minor ions (i.e. redundant ions from each clique) are removed from the dataset.

The majority of metabolites are MSI level 1 validation with authentic standards. The Amide-Neg method was a targeted acquisition and, as such, the transitions required for measuring all 101 compounds would have required authentic standards by default. For the HILIC-pos, C8-pos, and C18-neg methods 297 of 488 (60.9%) were confirmed with authentic standards (C18-neg: 88/88; C8-pos: 60/205; HILIC-pos 149/149). Therefore, in total, 398 of 589 (67.6%) were confirmed.

**Data Processing post data acquisition**

Pooled plasma QC samples were included throughout the assay after intervals of approximately 20 study samples. Metabolites with CV% > 25% or missing > 75% were excluded. Remaining missing values were imputed using the k-nearest-neighbor imputation method (R package "VIM"). Cluster number k was designated as 3. We examined the position of pooled plasma QC samples on principal component analysis (PCA) plots, to ensure they formed a tight cluster in the first two principal components (PCs). All metabolites were log-10 transformed and unit-scaled, and distribution of PCs according to demographic variables were examined to ensure these were not driving the PCs. Unnamed metabolites were removed, and datasets were restricted to those metabolites that were present in both GACRS and CAMP, resulting in a total of 589 metabolites for analysis (C8-pos n=205; C18-neg n=88; HILIC-pos n=195; Amide-neg n=101).

**Supplementary Results 1: Metabolite Associations within Phenotypic Domains of Asthma**

**Metabolite Associations with Clinical Traits of Asthma: Airway Hyperresponsive (AHR)**

There were 20 significant metabolite-AHR associations with 14 unique metabolites; 6 of the 14 metabolites (42.8%) were associated with both AHR phenotypes; 7 of the 14 significant metabolites were only associated with AHR phenotypes and therefore were AHR single-domain metabolites (**Table E1**). The strongest single-domain metabolites for AHR were involved in the purine (AMP, IMP, meta-p=0.0002 to 2.7x10-5), endocannabinoid (N-arachidonoyl dopamine, N-oleoyl dopamine, meta-p=9.7x10-5 to 7.6x10-5), TCA cycle (malic acid, meta-p=0.0001 to 8.7x10-5), and benzoate (hippurate, hippuric acid, meta-p=0.0005) metabolism. Metabolites involved in fatty acid metabolism (azelate, sebacate, 12,13-diHOME) had the most pathway-level associations with AHR and were significant across domains (meta-p=0.0002 to 1.35×10-6). Phosphocreatine (meta-p=1.0x10-5 to 8.94x10-7), aspartic acid (meta-p=1.0x10-5 to 8.94×10-7) and LPE(18:3) were significantly associated with AHR phenotypes and multi-domains, but were the only significant metabolites observed in their respective pathways.

**Metabolite Associations with Clinical Traits of Asthma: Atopy**

There were 5 significant metabolite-atopy associations among 4 unique metabolites (**Table E2**), including histamine, 1-methylhistamine, kynurenine, and niacinamide (meta-p=0.0003 to 4.70×10-8). All 4 of these metabolites were significant across other domains, and there were no single-domain metabolites.

**Metabolite Associations with Clinical Traits of Asthma: Lung Function**

The largest number of significant metabolite associations was observed with lung function phenotypes, with 216 significant metabolite-LF associations with 71 unique metabolites; 53 of the 71 metabolites (74.6%) were associated with at least 2 LF phenotypes; 41 of the 71 significant metabolites (57.7%) were only associated with LF phenotypes and therefore were LF single-domain metabolites (**Table E3**). The 71 metabolites that were significantly associated with lung function mainly consisted of 21 amino acids (meta-p=0.003 to 1.52×10-16) and 33 lipids (meta-p=0.003 to 8.86×10-11). Both amino acids and lipids were predominantly negatively associated with lung function (>70.0%). Multi-domain and single-domain metabolite-lung function phenotypes were observed in subpathways including glycolysis (glyceric acid and lactic acid), purine metabolism (uric acid, xanthosine), taurine (taurine), tryptophan (kynurenine, kynurenic acid, and indoleacetate), fatty acids (azelate, sebacate, 9,10-diHOME, and 12,13-diHOME), carnitines (C5:1 carnitine, C18 carnitine), and creatine metabolism (phosphocreatine, creatinine). The strongest overall associations were observed with lung function measures and vitamin A metabolite 9-cis-retinoic acid (meta-p= 3.04×10-15 to 1.52×10-16), glyceric acid (meta-p=2.14×10-16 to 1.57×10-16), and taurine (meta-p=1.52×10-14 to 2.03×10-13). Single-domain metabolites for lung function with the strongest associations include vitamin 9-cis-retinoic acid, xanthosine, C5:1 carnitine, cortisol, sphingolipids (SM(d18:1/16:1), Sphingosine-1-phosphate), phospholipids, vitamin B1 (Thiamine), and lysophospholipids (LPE(18:0/0:0), LPC(18:3), LPE(20:0), and LPE(20:1)).

**Metabolite Associations with Clinical Traits of Asthma: Th2 Inflammation**

There were 91 significant metabolite-Th2 Inflammation associations with 70 unique metabolites; 21 of the 70 metabolites (30.0%) were associated with both Th2 Inflammation phenotypes; 37 of the 70 significant metabolites (52.9%) were only associated with Th2 Inflammation phenotypes and therefore were Th2 Inflammation single-domain metabolites (**Table E4**). The 70 metabolites that were significantly associated with Th2 inflammation, mainly consisted of 53 lipids (meta-p=0.006 to 5.63×10-6). Of these lipid associations, 89.6% positively correlated with Th2 inflammation. Specific lipid classes had the most pathway-level associations with Th2 inflammation phenotypes, including 16 phosphatidylcholines (meta-p=0.006 to 7.82×10-6), 8 triacylglycerols (meta-p=0.001 to 0.006), 7 phosphatidylethanolamines (meta-p=0.006 to 5.65×10-6), and 6 lysophospholipids (meta-p=0.005 to 0.0002) were single-domain and had strong positive association with Th2 inflammation. Positive associations were observed between Th2 inflammation phenotypes and multi-domain metabolites including fatty acids (azelate, sebacate, 9,10-diHOME, and 12,13-diHOME), histamine (meta-p=8.37×10-11 to 1.74×10-15), 1-methylhistamine (meta-p= 1.28×10-8 to 3.51×10-12), as well as taurine (meta-p=2.49×10-6 to 7.55×10-11) and kynurenine (meta-p=5.88×10-9, 8.74×10-11). Carnitine and hemoglobin and porphyrin metabolites were single-domain and negatively associated with Th2 inflammation phenotypes (C16, C18:1, C18:2, C20:4, meta-p= 0.003 to 0.002).

**Metabolite Associations with Clinical Traits of Asthma: Non-Th2 Inflammation**

There were 53 significant metabolite-non-Th2 Inflammation associations with 41 unique metabolites; 12 of the 41 metabolites (29.3%) were associated with both non-Th2 Inflammation phenotypes; 33 of the 41 significant metabolites (80.5%) were only associated with non-Th2 Inflammation phenotypes and therefore were non-Th2 Inflammation single-domain metabolites (**Table E5**). These 41 metabolites, significantly associated with non-Th2 inflammation, mainly consisted of 18 amino acids (meta-p=0.004 to 1.15×10-5) and 19 lipids (meta-p=0.004 to 5.27×10-7). Amino acids were predominantly negatively associated (80.0%), while lipids were predominantly positively associated (83.3%) with non-Th2 inflammation. In amino acid sub-pathways, four metabolites each were found in tryptophan metabolism (indole-3-carboxylic acid, kynurenic acid, kynurenine, and xanthurenic acid) and the urea cycle; arginine and proline metabolism (arginine, citrulline, hydroxyproline, N-acetylornithine), three in histidine metabolism (anserine, histamine, histidine), and three in glycine, serine, and threonine metabolism (glycine, serine, threonine). Fatty acids (3-hydroxydecanoate, 16-hydroxypalmitate, hexadecanedioate, tetradecanedioate), long-chain monounsaturated fatty acids (myristoleic acid, nervonic acid, N-oleoyl taurine, oleoyl leucine), ceramides (Cer(d18:1/16:0)), sterols (CE(18:0)), alanine and aspartate (alanine, N-Acetyl-L-Aspartic acid) and TCA cycle (2-Hydroxybutyric acid, Succinic acid) metabolites were largely single-domain associations. The most pronounced negative associations with non-Th2 inflammation were with diacetylspermine (meta-p=1.83×10-7) and nervonic acid (meta-p=5.27×10-7). While some sub-pathways, like fatty acids (3-hydroxydecanoate, tetradecanedioate, hexadecanedioate, 16-hydroxypalmitate, and tetradecanedioate) and the TCA cycle (2-hydroxybutyric acid, succinic acid/methylmalonic acid, and 2-hydroxybutyric acid), were in the same direction as Th2 associations, non-Th2 associations with histamine, tryptophan, and carnitine (C4-OH carnitine) metabolites were in the opposite direction.

**Table E1: Association between Metabolites and Airway Hyperresponsive, adjusted for Age, Sex, BMI, Race, and ICS use (Combined Q-Value < 0.05 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **CAMP** | | **GACRS** | | **Combined** | | |
| **Clinical Marker** | **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Q-Value** |
| Ln(PC20) / Log10(PD20) | Aspartic acid | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000191 | -0.07 | 0.19 | -0.05 | 2.41E-06 | -0.05 | 8.94E-07 | 0.0002 |
| Ln(PC20) / Log10(PD20) | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -0.11 | 0.05 | -0.03 | 0.0009 | -0.04 | 0.0003 | 0.01 |
| Ln(PC20) / Log10(PD20) | N-Acetyl-L-Glutamine | Amino Acid | Glutamate Metabolism | HMDB0006029 | 0.01 | 0.79 | 0.04 | 8.88E-05 | 0.04 | 9.02E-05 | 0.007 |
| Ln(PC20) / Log10(PD20) | Malic acid\* | Energy | TCA Cycle | HMDB0000744 | -0.04 | 0.49 | -0.04 | 0.0002 | -0.04 | 0.0001 | 0.009 |
| Ln(PC20) / Log10(PD20) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | 0.01 | 0.89 | 0.04 | 0.0001 | 0.04 | 0.0001 | 0.008 |
| Ln(PC20) / Log10(PD20) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | 0.03 | 0.61 | 0.04 | 3.80E-05 | 0.04 | 3.04E-05 | 0.003 |
| Ln(PC20) / Log10(PD20) | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | 0.13 | 0.02 | 0.04 | 0.0001 | 0.04 | 2.41E-05 | 0.003 |
| Ln(PC20) / Log10(PD20) | IMP\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0011681 | -0.03 | 0.63 | -0.04 | 3.30E-05 | -0.04 | 2.69E-05 | 0.003 |
| Ln(PC20) / Log10(PD20) | AMP\* | Nucleotide | Purine Metabolism, Adenine containing | HMDB0000045 | -0.10 | 0.07 | -0.03 | 0.0007 | -0.03 | 0.0002 | 0.01 |
| PC20 >8 / PD20 >200 | Aspartic acid | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000191 | -0.13 | 0.14 | -1.08 | 3.40E-11 | -0.34 | 1.03E-05 | 0.002 |
| PC20 >8 / PD20 >200 | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -0.17 | 0.05 | -0.63 | 5.16E-07 | -0.32 | 8.55E-06 | 0.002 |
| PC20 >8 / PD20 >200 | Malic acid\* | Energy | TCA Cycle | HMDB0000744 | -0.07 | 0.41 | -0.51 | 6.14E-07 | -0.26 | 8.71E-05 | 0.007 |
| PC20 >8 / PD20 >200 | N-Arachidonoyl Dopamine\* | Lipid | Endocannabinoid | KEGG C12271 | 0.28 | 0.002 | 0.24 | 0.02 | 0.26 | 9.74E-05 | 0.007 |
| PC20 >8 / PD20 >200 | N-Oleoyl Dopamine\* | Lipid | Endocannabinoid | CAS:105955-11-1 | 0.38 | 8.93E-05 | 0.16 | 0.10 | 0.27 | 7.57E-05 | 0.007 |
| PC20 >8 / PD20 >200 | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | 0.08 | 0.36 | 0.70 | 1.48E-07 | 0.28 | 0.0002 | 0.01 |
| PC20 >8 / PD20 >200 | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | 0.15 | 0.09 | 0.74 | 2.27E-09 | 0.34 | 1.35E-06 | 0.0008 |
| PC20 >8 / PD20 >200 | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | 0.10 | 0.23 | 0.71 | 1.49E-09 | 0.31 | 6.43E-06 | 0.002 |
| PC20 >8 / PD20 >200 | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | 0.15 | 0.08 | 0.69 | 1.94E-07 | 0.32 | 1.43E-05 | 0.007 |
| PC20 >8 / PD20 >200 | Hippurate\* | Xenobiotics | Benzoate Metabolism | HMDB0000714 | 0.25 | 0.004 | 0.19 | 0.05 | 0.22 | 0.0005 | 0.03 |
| PC20 >8 / PD20 >200 | Hippuric acid\* | Xenobiotics | Benzoate Metabolism | HMDB0000714 | 0.26 | 0.003 | 0.18 | 0.06 | 0.23 | 0.0005 | 0.03 |

\*refers to single-domain metabolites. Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E2: Association between Metabolites and Atopy, adjusted for Age, Sex, BMI, Race, and ICS use (Combined Q-Value < 0.05 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **CAMP** | | **GACRS** | | **Combined** | | |
| **Clinical Marker** | **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Q-Value** |
| Log10(IgE) | 1-Methylhistamine | Amino Acid | Histidine Metabolism | HMDB0000898 | 0.12 | 6.54E-07 | 0.06 | 0.003 | 0.08 | 4.70E-08 | 2.77E-05 |
| Log10(IgE) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 0.06 | 0.005 | 0.08 | 5.12E-05 | 0.07 | 9.55E-07 | 0.0003 |
| Log10(IgE) | Niacinamide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0001406 | 0.07 | 0.001 | 0.04 | 0.05 | 0.05 | 0.0003 | 0.04 |
| Log10(IgE) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | 0.03 | 0.24 | 0.09 | 7.53E-06 | 0.06 | 2.84E-05 | 0.006 |
| Log10(IgE) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 0.28 | 0.005 | 0.27 | 0.001 | 0.27 | 1.89E-05 | 0.01 |
| Skin Prick Test (Binary) | 1-Methylhistamine | Amino Acid | Histidine Metabolism | HMDB0000898 | 0.12 | 6.54E-07 | 0.06 | 0.003 | 0.08 | 4.70E-08 | 2.77E-05 |

\*refers to single-domain metabolites. Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E3: Association between Metabolites and Lung Function (Meta Q-Value < 0.05), adjusted for Age, Sex, BMI, Race, ICS use, and Height (Combined Q-Value < 0.05 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **CAMP** | | **GACRS** | | **Combined** | | |
| **Clinical Marker** | **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Q-Value** |
| FVC (Pre BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | 0.02 | 0.09 | 0.03 | 0.0009 | 0.03 | 0.0002 | 0.006 |
| FVC (Pre BD) | Creatinine\* | Amino Acid | Creatine Metabolism | HMDB0000562 | 0.08 | 3.16E-06 | 0.02 | 0.03 | 0.04 | 2.60E-05 | 0.001 |
| FVC (Pre BD) | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -0.02 | 0.17 | -0.04 | 1.93E-05 | -0.03 | 1.34E-05 | 0.0006 |
| FVC (Pre BD) | GABA\* | Amino Acid | Glutamate Metabolism | HMDB0000112 | -0.06 | 6.20E-05 | -0.01 | 0.15 | -0.03 | 0.0009 | 0.02 |
| FVC (Pre BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | 0.05 | 0.0006 | 0.02 | 0.007 | 0.03 | 3.83E-05 | 0.001 |
| FVC (Pre BD) | DMGV\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0240212 | -0.08 | 1.75E-07 | -0.01 | 0.55 | -0.03 | 0.001 | 0.02 |
| FVC (Pre BD) | Indoleacetate\* | Amino Acid | Tryptophan Metabolism | HMDB0000197 | -0.10 | 2.84E-11 | -0.02 | 0.06 | -0.04 | 2.26E-07 | 1.94E-05 |
| FVC (Pre BD) | Acetyl-galactosamine\* | Carbohydrate | Aminosugar Metabolism | HMDB0000853 | -0.06 | 8.06E-05 | -0.01 | 0.26 | -0.02 | 0.002 | 0.04 |
| FVC (Pre BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | 0.03 | 0.06 | 0.05 | 2.58E-09 | 0.05 | 1.39E-09 | 4.11E-07 |
| FVC (Pre BD) | Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -0.01 | 0.56 | -0.03 | 0.0003 | -0.03 | 0.0008 | 0.02 |
| FVC (Pre BD) | 9-cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | 0.04 | 0.005 | 0.05 | 1.26E-08 | 0.05 | 2.18E-10 | 1.29E-07 |
| FVC (Pre BD) | Thiamine\* | Cofactors and Vitamins | Vitamin B1 Metabolism | HMDB0000235 | -0.05 | 0.001 | -0.04 | 5.24E-05 | -0.04 | 2.31E-07 | 1.94E-05 |
| FVC (Pre BD) | C18 carnitine\* | Lipid | Carnitine Metabolism | HMDB0000848 | 0.05 | 0.001 | 0.03 | 0.0003 | 0.04 | 1.61E-06 | 0.0001 |
| FVC (Pre BD) | C18:1 carnitine | Lipid | Carnitine Metabolism | HMDB0005065 | 0.05 | 0.001 | 0.02 | 0.07 | 0.02 | 0.001 | 0.02 |
| FVC (Pre BD) | C20:4 carnitine | Lipid | Carnitine Metabolism | HMDB0006455 | 0.06 | 7.09E-05 | 0.01 | 0.23 | 0.02 | 0.002 | 0.03 |
| FVC (Pre BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | 0.04 | 0.01 | 0.04 | 1.12E-05 | 0.04 | 3.63E-07 | 2.67E-05 |
| FVC (Pre BD) | Cortisol\* | Lipid | Corticosteroids | HMDB0000063 | -0.10 | 2.84E-11 | -0.02 | 0.06 | -0.04 | 2.26E-07 | 1.94E-05 |
| FVC (Pre BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | 0.01 | 0.43 | 0.04 | 3.14E-05 | 0.03 | 7.91E-05 | 0.003 |
| FVC (Pre BD) | Dodecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000623 | -0.08 | 1.75E-07 | -0.01 | 0.55 | -0.03 | 0.001 | 0.02 |
| FVC (Pre BD) | Hydroxymyristate\* | Lipid | Fatty Acid Metabolism | HMDB0002261 | -0.06 | 6.20E-05 | -0.01 | 0.15 | -0.03 | 0.0009 | 0.02 |
| FVC (Pre BD) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | 0.01 | 0.98 | 0.05 | 1.41E-07 | 0.03 | 9.08E-06 | 0.0005 |
| FVC (Pre BD) | N-Oleoyl Taurine | Lipid | Long Chain Monounsaturated Fatty Acid | CAS:52514-04-2 | -0.03 | 0.04 | -0.02 | 0.009 | -0.02 | 0.001 | 0.02 |
| FVC (Pre BD) | N-Palmitoyl Taurine | Lipid | Long Chain Saturated Fatty Acid | CAS:83982-06-3 | -0.01 | 0.36 | -0.03 | 0.004 | -0.02 | 0.003 | 0.05 |
| FVC (Pre BD) | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | 0.01 | 0.36 | 0.04 | 3.61E-06 | 0.03 | 9.79E-06 | 0.0005 |
| FVC (Pre BD) | LPE(18:0)\_B\* | Lipid | Lysophospholipid | HMDB0011130 | 0.04 | 0.006 | 0.02 | 0.05 | 0.02 | 0.002 | 0.03 |
| FVC (Pre BD) | LPE(20:0)\* | Lipid | Lysophospholipid | HMDB0011511 | 0.04 | 0.002 | 0.02 | 0.07 | 0.02 | 0.002 | 0.03 |
| FVC (Pre BD) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | 0.03 | 0.02 | 0.03 | 0.0004 | 0.03 | 2.64E-05 | 0.001 |
| FVC (Pre BD) | SM(d18:1/16:1)\* | Lipid | Sphingolipids | HMDB0029216 | -0.10 | 2.84E-11 | -0.02 | 0.06 | -0.04 | 2.26E-07 | 1.94E-05 |
| FVC (Pre BD) | SM(d18:1/18:1)\* | Lipid | Sphingolipids | HMDB0012101 | -0.08 | 1.75E-07 | -0.01 | 0.55 | -0.03 | 0.001 | 0.02 |
| FVC (Pre BD) | SM(d18:1/22:1)\* | Lipid | Sphingolipids | HMDB0012104 | -0.06 | 6.20E-05 | -0.01 | 0.15 | -0.03 | 0.0009 | 0.02 |
| FVC (Pre BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | -0.03 | 0.07 | -0.02 | 0.01 | -0.02 | 0.002 | 0.03 |
| FVC (Pre BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | 0.04 | 0.002 | 0.04 | 2.22E-05 | 0.04 | 1.66E-07 | 1.94E-05 |
| FVC (Post BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | 0.03 | 0.04 | 0.03 | 0.004 | 0.03 | 0.0004 | 0.01 |
| FVC (Post BD) | Creatinine\* | Amino Acid | Creatine Metabolism | HMDB0000562 | 0.08 | 9.80E-06 | 0.02 | 0.01 | 0.04 | 1.65E-05 | 0.0006 |
| FVC (Post BD) | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -0.02 | 0.09 | -0.03 | 0.004 | -0.02 | 0.0008 | 0.02 |
| FVC (Post BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | 0.05 | 0.0002 | 0.03 | 0.003 | 0.03 | 5.53E-06 | 0.0003 |
| FVC (Post BD) | DMGV\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0240212 | -0.08 | 2.82E-07 | 0.01 | 0.77 | -0.02 | 0.003 | 0.05 |
| FVC (Post BD) | Glycine | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000123 | 0.02 | 0.25 | 0.03 | 0.004 | 0.02 | 0.002 | 0.04 |
| FVC (Post BD) | Indoleacetate\* | Amino Acid | Tryptophan Metabolism | HMDB0000197 | -0.09 | 2.19E-10 | -0.02 | 0.06 | -0.04 | 5.25E-07 | 4.42E-05 |
| FVC (Post BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | 0.03 | 0.01 | 0.06 | 3.28E-10 | 0.05 | 2.32E-11 | 6.83E-09 |
| FVC (Post BD) | Lactic acid\* | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000190 | 0.04 | 0.002 | 0.02 | 0.009 | 0.03 | 0.0001 | 0.004 |
| FVC (Post BD) | Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -0.01 | 0.58 | -0.03 | 0.0005 | -0.02 | 0.001 | 0.03 |
| FVC (Post BD) | 9-cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | 0.04 | 0.002 | 0.06 | 6.49E-10 | 0.05 | 3.89E-12 | 2.29E-09 |
| FVC (Post BD) | Thiamine\* | Cofactors and Vitamins | Vitamin B1 Metabolism | HMDB0000235 | -0.05 | 0.002 | -0.03 | 9.63E-05 | -0.04 | 6.83E-07 | 5.03E-05 |
| FVC (Post BD) | C18 carnitine\* | Lipid | Carnitine Metabolism | HMDB0000848 | 0.05 | 0.0009 | 0.03 | 0.003 | 0.03 | 1.66E-05 | 0.0006 |
| FVC (Post BD) | C18:1 carnitine | Lipid | Carnitine Metabolism | HMDB0005065 | 0.04 | 0.001 | 0.01 | 0.11 | 0.02 | 0.002 | 0.04 |
| FVC (Post BD) | C20:4 carnitine | Lipid | Carnitine Metabolism | HMDB0006455 | 0.06 | 5.93E-06 | 0.01 | 0.25 | 0.03 | 0.0007 | 0.02 |
| FVC (Post BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | 0.04 | 0.003 | 0.04 | 5.22E-06 | 0.04 | 5.09E-08 | 7.50E-06 |
| FVC (Post BD) | Cortisol\* | Lipid | Corticosteroids | HMDB0000063 | -0.09 | 2.19E-10 | -0.02 | 0.06 | -0.04 | 5.25E-07 | 4.42E-05 |
| FVC (Post BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | 0.01 | 0.57 | 0.05 | 1.24E-07 | 0.04 | 1.69E-06 | 9.98E-05 |
| FVC (Post BD) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | 0.02 | 0.26 | 0.03 | 0.002 | 0.02 | 0.001 | 0.03 |
| FVC (Post BD) | Dodecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000623 | -0.08 | 2.82E-07 | 0.01 | 0.77 | -0.02 | 0.003 | 0.05 |
| FVC (Post BD) | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | 0.01 | 0.37 | 0.04 | 9.71E-07 | 0.03 | 3.49E-06 | 0.0002 |
| FVC (Post BD) | LPE(20:0)\* | Lipid | Lysophospholipid | HMDB0011511 | 0.05 | 0.002 | 0.02 | 0.08 | 0.02 | 0.002 | 0.03 |
| FVC (Post BD) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | 0.03 | 0.02 | 0.03 | 0.0001 | 0.03 | 6.38E-06 | 0.0003 |
| FVC (Post BD) | Cholic acid\* | Lipid | Primary Bile Acid Metabolism | HMDB0000619 | 0.02 | 0.10 | 0.02 | 0.01 | 0.02 | 0.002 | 0.04 |
| FVC (Post BD) | SM(d18:1/16:1)\* | Lipid | Sphingolipids | HMDB0029216 | -0.09 | 2.19E-10 | -0.02 | 0.06 | -0.04 | 5.25E-07 | 4.42E-05 |
| FVC (Post BD) | SM(d18:1/18:1)\* | Lipid | Sphingolipids | HMDB0012101 | -0.08 | 2.82E-07 | 0.01 | 0.77 | -0.02 | 0.003 | 0.05 |
| FVC (Post BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | -0.03 | 0.01 | -0.03 | 0.005 | -0.03 | 0.0002 | 0.005 |
| FVC (Post BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | 0.05 | 0.0007 | 0.04 | 1.83E-06 | 0.04 | 4.32E-09 | 8.48E-07 |
| FEV1 (Pre BD) | Indoleacetate\* | Amino Acid | Tryptophan Metabolism | HMDB0000197 | -0.06 | 8.35E-06 | -0.01 | 0.12 | -0.03 | 0.0002 | 0.04 |
| FEV1 (Pre BD) | Cortisol\* | Lipid | Corticosteroids | HMDB0000063 | -0.06 | 8.35E-06 | -0.01 | 0.12 | -0.03 | 0.0002 | 0.04 |
| FEV1 (Pre BD) | SM(d18:1/16:1)\* | Lipid | Sphingolipids | HMDB0029216 | -0.06 | 8.35E-06 | -0.01 | 0.12 | -0.03 | 0.0002 | 0.04 |
| FEV1 (Post BD) | Creatinine\* | Amino Acid | Creatine Metabolism | HMDB0000562 | 0.06 | 0.0002 | 0.02 | 0.05 | 0.03 | 0.0004 | 0.03 |
| FEV1 (Post BD) | Indoleacetate\* | Amino Acid | Tryptophan Metabolism | HMDB0000197 | -0.07 | 2.76E-07 | -0.01 | 0.10 | -0.03 | 1.96E-05 | 0.004 |
| FEV1 (Post BD) | Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -0.02 | 0.08 | -0.03 | 0.001 | -0.02 | 0.0002 | 0.03 |
| FEV1 (Post BD) | Thiamine\* | Cofactors and Vitamins | Vitamin B1 Metabolism | HMDB0000235 | -0.05 | 1.68E-05 | -0.02 | 0.03 | -0.03 | 3.26E-05 | 0.005 |
| FEV1 (Post BD) | C18 carnitine\* | Lipid | Carnitine Metabolism | HMDB0000848 | 0.04 | 0.002 | 0.02 | 0.02 | 0.02 | 0.0003 | 0.03 |
| FEV1 (Post BD) | Cortisol\* | Lipid | Corticosteroids | HMDB0000063 | -0.07 | 2.76E-07 | -0.01 | 0.10 | -0.03 | 1.96E-05 | 0.004 |
| FEV1 (Post BD) | SM(d18:1/16:1)\* | Lipid | Sphingolipids | HMDB0029216 | -0.07 | 2.76E-07 | -0.01 | 0.10 | -0.03 | 1.96E-05 | 0.004 |
| FEV1 (Post BD) | N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | -0.01 | 0.52 | -0.03 | 0.0003 | -0.02 | 0.0007 | 0.04 |
| FEV1/FVC (Pre BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | -0.67 | 0.03 | -0.98 | 4.92E-05 | -0.86 | 5.03E-06 | 0.0002 |
| FEV1/FVC (Pre BD) | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | 0.09 | 0.77 | 0.83 | 0.0004 | 0.54 | 0.003 | 0.04 |
| FEV1/FVC (Pre BD) | N-Acetyl-L-Glutamine | Amino Acid | Glutamate Metabolism | HMDB0006029 | -0.01 | 0.97 | -1.06 | 9.20E-06 | -0.65 | 0.0005 | 0.01 |
| FEV1/FVC (Pre BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | -0.99 | 0.001 | -0.86 | 0.0002 | -0.90 | 8.07E-07 | 4.32E-05 |
| FEV1/FVC (Pre BD) | Glycine | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000123 | -0.27 | 0.38 | -0.77 | 0.002 | -0.58 | 0.002 | 0.04 |
| FEV1/FVC (Pre BD) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | -0.83 | 0.005 | -0.64 | 0.005 | -0.72 | 8.65E-05 | 0.003 |
| FEV1/FVC (Pre BD) | 2-Ketoisovaleric acid KIV\* | Amino Acid | Leucine, Isoleucine and Valine Metabolism | HMDB0000019 | 0.79 | 0.007 | 0.54 | 0.02 | 0.63 | 0.0005 | 0.01 |
| FEV1/FVC (Pre BD) | Formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | -0.51 | 0.09 | -0.66 | 0.005 | -0.60 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -0.68 | 0.02 | -1.88 | 3.00E-15 | -1.41 | 1.52E-14 | 2.98E-12 |
| FEV1/FVC (Pre BD) | Acisoga\* | Amino Acid | Polyamine Metabolism | HMDB0061384 | -0.24 | 0.41 | -0.81 | 0.0005 | -0.59 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -0.67 | 0.02 | -0.55 | 0.02 | -0.60 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.54 | 0.08 | -1.11 | 1.88E-06 | -0.90 | 1.03E-06 | 5.07E-05 |
| FEV1/FVC (Pre BD) | Hydroxyproline | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000725 | -0.34 | 0.28 | -0.68 | 0.004 | -0.56 | 0.003 | 0.05 |
| FEV1/FVC (Pre BD) | Ornithine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000214 | -0.72 | 0.02 | -0.71 | 0.002 | -0.71 | 0.0001 | 0.004 |
| FEV1/FVC (Pre BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -0.79 | 0.008 | -1.96 | 1.70E-16 | -1.51 | 2.14E-16 | 6.29E-14 |
| FEV1/FVC (Pre BD) | NMMA\* | Cofactors and Vitamins | Nitric Oxide Biosynthesis | HMDB0029416 | -0.16 | 0.60 | -0.87 | 0.0002 | -0.60 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | 9-Cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | -0.84 | 0.004 | -1.96 | 3.41E-16 | -1.52 | 1.52E-16 | 6.29E-14 |
| FEV1/FVC (Pre BD) | Glyoxylic Acid\* | Energy | TCA Cycle | HMDB0000119 | 0.56 | 0.06 | 0.56 | 0.02 | 0.56 | 0.002 | 0.03 |
| FEV1/FVC (Pre BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | -0.98 | 0.001 | -1.20 | 3.94E-07 | -1.12 | 1.45E-09 | 9.51E-08 |
| FEV1/FVC (Pre BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -0.48 | 0.11 | -1.52 | 1.14E-10 | -1.13 | 8.94E-10 | 6.58E-08 |
| FEV1/FVC (Pre BD) | 3-Methyladipate | Lipid | Fatty Acid Metabolism | HMDB0000555 | -0.03 | 0.91 | -1.04 | 8.83E-06 | -0.65 | 0.0004 | 0.009 |
| FEV1/FVC (Pre BD) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | -0.65 | 0.03 | -0.83 | 0.0004 | -0.76 | 3.18E-05 | 0.001 |
| FEV1/FVC (Pre BD) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | -0.13 | 0.66 | -1.85 | 5.31E-15 | -1.19 | 8.86E-11 | 1.04E-08 |
| FEV1/FVC (Pre BD) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | -0.10 | 0.74 | -1.64 | 6.32E-12 | -1.03 | 1.85E-08 | 1.09E-06 |
| FEV1/FVC (Pre BD) | Arachidonate\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | 0.26 | 0.37 | 0.81 | 0.0005 | 0.60 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Arachidonic acid | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | 0.54 | 0.07 | 0.72 | 0.002 | 0.65 | 0.0004 | 0.009 |
| FEV1/FVC (Pre BD) | Stearic acid\* | Lipid | Long Chain Saturated Fatty Acid | HMDB0000827 | 0.42 | 0.17 | 0.93 | 6.10E-05 | 0.74 | 5.26E-05 | 0.002 |
| FEV1/FVC (Pre BD) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | -0.18 | 0.55 | -0.82 | 0.0004 | -0.59 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | PC(P-36:0)/PC(O-36:1) | Lipid | Phosphatidylcholine | HMDB0011241 | -0.42 | 0.17 | -0.71 | 0.004 | -0.60 | 0.002 | 0.03 |
| FEV1/FVC (Pre BD) | PE(P-36:3)/PE(O-36:4) | Lipid | Phosphatidylethanolamine | HMDB0011442 | -0.78 | 0.01 | -0.42 | 0.08 | -0.55 | 0.003 | 0.05 |
| FEV1/FVC (Pre BD) | Choline\* | Lipid | Phospholipid Metabolism | HMDB0000097 | -1.06 | 0.0004 | -0.59 | 0.01 | -0.77 | 2.44E-05 | 0.001 |
| FEV1/FVC (Pre BD) | Trimethylamine-N-oxide\* | Lipid | Phospholipid Metabolism | HMDB0000925 | -0.57 | 0.05 | -0.59 | 0.01 | -0.58 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Taurodeoxycholic acid / Taurochenodeoxycholic acid\* | Lipid | Secondary Bile Acid Metabolism | HMDB0000896 | -0.53 | 0.08 | -0.65 | 0.006 | -0.60 | 0.001 | 0.02 |
| FEV1/FVC (Pre BD) | Sphingosine-1-phosphate\* | Lipid | Sphingolipids | HMDB0000277 | -0.66 | 0.03 | -0.79 | 0.0007 | -0.74 | 5.75E-05 | 0.002 |
| FEV1/FVC (Pre BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 0.94 | 0.0021 | 1.41 | 2.15E-09 | 1.23 | 2.03E-11 | 2.99E-09 |
| FEV1/FVC (Pre BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | -0.82 | 0.005 | -1.31 | 1.67E-08 | -1.12 | 5.74E-10 | 4.83E-08 |
| FEV1/FVC (Pre BD) | 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -0.83 | 0.005 | -0.61 | 0.008 | -0.69 | 0.0001 | 0.004 |
| FEV1/FVC (Pre BD) | Sulfamethoxazole\* | Xenobiotics | Drug | HMDB0015150 | 0.22 | 0.45 | 0.72 | 0.002 | 0.53 | 0.003 | 0.05 |
| FEV1/FVC (Post BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | -0.52 | 0.03 | -0.50 | 0.02 | -0.51 | 0.001 | 0.03 |
| FEV1/FVC (Post BD) | Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | 0.23 | 0.32 | 0.67 | 0.001 | 0.48 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | -0.88 | 0.0003 | -0.71 | 0.0004 | -0.78 | 3.98E-07 | 2.13E-05 |
| FEV1/FVC (Post BD) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | -0.47 | 0.04 | -0.44 | 0.03 | -0.45 | 0.003 | 0.04 |
| FEV1/FVC (Post BD) | 2-Ketoisovaleric acid KIV\* | Amino Acid | Leucine, Isoleucine and Valine Metabolism | HMDB0000019 | 0.78 | 0.0008 | 0.40 | 0.05 | 0.56 | 0.0002 | 0.006 |
| FEV1/FVC (Post BD) | Formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | -0.36 | 0.13 | -0.57 | 0.005 | -0.48 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -0.50 | 0.03 | -1.62 | 6.89E-15 | -1.13 | 2.03E-13 | 3.99E-11 |
| FEV1/FVC (Post BD) | Acisoga\* | Amino Acid | Polyamine Metabolism | HMDB0061384 | -0.05 | 0.83 | -0.88 | 1.43E-05 | -0.52 | 0.0006 | 0.01 |
| FEV1/FVC (Post BD) | Diacetylspermine | Amino Acid | Polyamine Metabolism | HMDB0002172 | -0.53 | 0.03 | -0.47 | 0.03 | -0.49 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -0.39 | 0.10 | -0.61 | 0.003 | -0.52 | 0.0008 | 0.02 |
| FEV1/FVC (Post BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.50 | 0.04 | -0.99 | 1.12E-06 | -0.79 | 3.55E-07 | 2.09E-05 |
| FEV1/FVC (Post BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -0.91 | 0.0001 | -1.56 | 7.60E-14 | -1.27 | 1.57E-16 | 9.26E-14 |
| FEV1/FVC (Post BD) | Lactic acid\* | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000190 | -0.88 | 0.0002 | -0.54 | 0.009 | -0.68 | 1.12E-05 | 0.0005 |
| FEV1/FVC (Post BD) | Pyruvic acid\* | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000243 | -0.36 | 0.13 | -0.53 | 0.009 | -0.45 | 0.003 | 0.04 |
| FEV1/FVC (Post BD) | 9-Cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | -0.72 | 0.002 | -1.62 | 1.22E-14 | -1.23 | 3.04E-15 | 8.96E-13 |
| FEV1/FVC (Post BD) | Glyoxylic Acid\* | Energy | TCA Cycle | HMDB0000119 | 0.50 | 0.03 | 0.48 | 0.02 | 0.49 | 0.001 | 0.03 |
| FEV1/FVC (Post BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | -0.83 | 0.0004 | -1.03 | 8.02E-07 | -0.94 | 1.37E-09 | 1.15E-07 |
| FEV1/FVC (Post BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -0.52 | 0.03 | -1.34 | 8.21E-11 | -0.99 | 1.55E-10 | 1.83E-08 |
| FEV1/FVC (Post BD) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | -0.53 | 0.03 | -0.72 | 0.0004 | -0.64 | 3.12E-05 | 0.001 |
| FEV1/FVC (Post BD) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | -0.01 | 0.96 | -1.49 | 7.28E-13 | -0.85 | 4.18E-08 | 2.73E-06 |
| FEV1/FVC (Post BD) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | -0.10 | 0.67 | -1.31 | 4.62E-10 | -0.77 | 6.50E-07 | 3.19E-05 |
| FEV1/FVC (Post BD) | 20-Hydroxy-N-Arachidonoyl Taurine\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | Pubchem 53394637 | -0.31 | 0.18 | -0.72 | 0.0004 | -0.54 | 0.0004 | 0.01 |
| FEV1/FVC (Post BD) | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | -0.11 | 0.65 | -1.07 | 2.65E-07 | -0.66 | 2.32E-05 | 0.0009 |
| FEV1/FVC (Post BD) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | -0.21 | 0.39 | -0.68 | 0.001 | -0.48 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | PC(36:4-OH)\* | Lipid | Phosphatidylcholine |  | -0.42 | 0.07 | -0.54 | 0.008 | -0.49 | 0.001 | 0.03 |
| FEV1/FVC (Post BD) | Choline\* | Lipid | Phospholipid Metabolism | HMDB0000097 | -0.91 | 0.0001 | -0.53 | 0.009 | -0.69 | 6.33E-06 | 0.0003 |
| FEV1/FVC (Post BD) | Trimethylamine-N-oxide\* | Lipid | Phospholipid Metabolism | HMDB0000925 | -0.54 | 0.02 | -0.40 | 0.05 | -0.46 | 0.003 | 0.04 |
| FEV1/FVC (Post BD) | Taurodeoxycholic acid / Taurochenodeoxycholic acid\* | Lipid | Secondary Bile Acid Metabolism | HMDB0000896 | -0.57 | 0.02 | -0.60 | 0.004 | -0.59 | 0.0002 | 0.006 |
| FEV1/FVC (Post BD) | Sphingosine-1-phosphate\* | Lipid | Sphingolipids | HMDB0000277 | -0.64 | 0.008 | -0.51 | 0.01 | -0.57 | 0.0003 | 0.008 |
| FEV1/FVC (Post BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 0.80 | 0.0008 | 0.98 | 2.10E-06 | 0.90 | 6.18E-09 | 4.55E-07 |
| FEV1/FVC (Post BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | -0.80 | 0.0006 | -1.09 | 8.31E-08 | -0.96 | 2.65E-10 | 2.60E-08 |
| FEV1/FVC (Post BD) | Adenine | Nucleotide | Purine Metabolism, Adenine containing | HMDB0000034 | -0.01 | 0.98 | -1.01 | 8.76E-07 | -0.57 | 0.0002 | 0.006 |
| FEV1/FVC (Post BD) | N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | -0.27 | 0.28 | -0.63 | 0.002 | -0.48 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | Phenylacetylglutamine\* | Peptide | Acetylated Peptides | HMDB0006344 | -0.38 | 0.11 | -0.56 | 0.006 | -0.48 | 0.002 | 0.03 |
| FEV1/FVC (Post BD) | 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -0.54 | 0.02 | -0.60 | 0.003 | -0.58 | 0.0002 | 0.006 |
| FEF25-75 (Pre BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -0.05 | 0.05 | -0.08 | 2.59E-05 | -0.07 | 4.60E-06 | 0.0009 |
| FEF25-75 (Pre BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.05 | 0.06 | -0.08 | 7.40E-06 | -0.07 | 1.86E-06 | 0.0006 |
| FEF25-75 (Pre BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -0.05 | 0.05 | -0.07 | 8.82E-05 | -0.07 | 1.42E-05 | 0.002 |
| FEF25-75 (Pre BD) | 9-cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | -0.04 | 0.10 | -0.07 | 0.0001 | -0.06 | 4.07E-05 | 0.005 |
| FEF25-75 (Pre BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -0.04 | 0.16 | -0.06 | 0.001 | -0.05 | 0.0006 | 0.04 |
| FEF25-75 (Pre BD) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | -0.01 | 0.59 | -0.07 | 7.37E-05 | -0.05 | 0.0004 | 0.03 |
| FEF25-75 (Pre BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 0.06 | 0.02 | 0.08 | 4.46E-05 | 0.07 | 2.19E-06 | 0.0006 |
| FEF25-75 (Pre BD) | N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | -0.04 | 0.14 | -0.06 | 0.001 | -0.05 | 0.0005 | 0.03 |
| FEF25-75 (Pre BD) | 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -0.06 | 0.02 | -0.05 | 0.007 | -0.05 | 0.0003 | 0.03 |
| FEF25-75 (Post BD) | Aspartic acid | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000191 | 0.03 | 0.23 | 0.07 | 0.0002 | 0.06 | 0.0003 | 0.02 |
| FEF25-75 (Post BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -0.05 | 0.07 | -0.07 | 0.0006 | -0.06 | 0.0001 | 0.02 |
| FEF25-75 (Post BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.05 | 0.06 | -0.08 | 2.79E-05 | -0.07 | 6.27E-06 | 0.004 |
| FEF25-75 (Post BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -0.07 | 0.006 | -0.05 | 0.005 | -0.06 | 8.52E-05 | 0.02 |
| FEF25-75 (Post BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 0.05 | 0.05 | 0.06 | 0.002 | 0.06 | 0.0002 | 0.02 |
| FEF25-75 (Post BD) | N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | -0.04 | 0.15 | -0.08 | 1.86E-05 | -0.07 | 1.48E-05 | 0.004 |
| FEF25-75 (Post BD) | Pseudouridine\* | Nucleotide | Pyrimidine Metabolism, Uracil containing | HMDB0000767 | -0.04 | 0.13 | -0.06 | 0.0007 | -0.05 | 0.0003 | 0.02 |
| FEF25-75/FVC (Pre BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | -1.87 | 0.02 | -4.31 | 3.96E-06 | -2.93 | 1.71E-06 | 9.14E-05 |
| FEF25-75/FVC (Pre BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | -2.39 | 0.003 | -2.51 | 0.005 | -2.44 | 4.94E-05 | 0.002 |
| FEF25-75/FVC (Pre BD) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | -1.88 | 0.02 | -2.02 | 0.02 | -1.94 | 0.001 | 0.03 |
| FEF25-75/FVC (Pre BD) | 2-ketoisovaleric acid KIV\* | Amino Acid | Leucine, Isoleucine and Valine Metabolism | HMDB0000019 | 2.07 | 0.009 | 1.69 | 0.06 | 1.91 | 0.001 | 0.03 |
| FEF25-75/FVC (Pre BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -1.42 | 0.08 | -6.70 | 4.84E-13 | -3.71 | 7.95E-10 | 1.56E-07 |
| FEF25-75/FVC (Pre BD) | Acisoga\* | Amino Acid | Polyamine Metabolism | HMDB0061384 | -1.00 | 0.20 | -3.05 | 0.0007 | -1.89 | 0.001 | 0.03 |
| FEF25-75/FVC (Pre BD) | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -1.82 | 0.02 | -2.27 | 0.01 | -2.02 | 0.0007 | 0.02 |
| FEF25-75/FVC (Pre BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -1.90 | 0.02 | -4.36 | 1.30E-06 | -3.01 | 5.76E-07 | 3.39E-05 |
| FEF25-75/FVC (Pre BD) | Ornithine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000214 | -1.56 | 0.06 | -2.99 | 0.0009 | -2.22 | 0.0003 | 0.01 |
| FEF25-75/FVC (Pre BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -1.80 | 0.02 | -6.94 | 6.41E-14 | -4.01 | 2.25E-11 | 6.64E-09 |
| FEF25-75/FVC (Pre BD) | 9-Cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | -2.03 | 0.01 | -6.82 | 2.55E-13 | -4.06 | 1.30E-11 | 6.64E-09 |
| FEF25-75/FVC (Pre BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | -2.73 | 0.0006 | -4.67 | 3.82E-07 | -3.57 | 2.73E-09 | 3.22E-07 |
| FEF25-75/FVC (Pre BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -1.53 | 0.06 | -5.26 | 8.40E-09 | -3.18 | 1.29E-07 | 1.09E-05 |
| FEF25-75/FVC (Pre BD) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | -1.94 | 0.02 | -2.54 | 0.005 | -2.20 | 0.0002 | 0.008 |
| FEF25-75/FVC (Pre BD) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | -0.46 | 0.56 | -6.52 | 1.34E-12 | -3.08 | 2.60E-07 | 1.91E-05 |
| FEF25-75/FVC (Pre BD) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | -0.34 | 0.67 | -5.86 | 2.25E-10 | -2.70 | 6.61E-06 | 0.0003 |
| FEF25-75/FVC (Pre BD) | Arachidonate\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | 0.44 | 0.58 | 3.59 | 7.12E-05 | 1.81 | 0.002 | 0.05 |
| FEF25-75/FVC (Pre BD) | Arachidonic acid | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | 1.25 | 0.11 | 3.05 | 0.0008 | 2.04 | 0.0006 | 0.02 |
| FEF25-75/FVC (Pre BD) | Stearic acid\* | Lipid | Long Chain Saturated Fatty Acid | HMDB0000827 | 1.16 | 0.16 | 3.32 | 0.0002 | 2.14 | 0.0004 | 0.01 |
| FEF25-75/FVC (Pre BD) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | -0.82 | 0.32 | -3.27 | 0.0003 | -1.93 | 0.002 | 0.03 |
| FEF25-75/FVC (Pre BD) | Choline\* | Lipid | Phospholipid Metabolism | HMDB0000097 | -2.84 | 0.0004 | -2.37 | 0.008 | -2.63 | 1.04E-05 | 0.0005 |
| FEF25-75/FVC (Pre BD) | Trimethylamine-N-oxide\* | Lipid | Phospholipid Metabolism | HMDB0000925 | -1.52 | 0.05 | -2.59 | 0.004 | -1.99 | 0.0008 | 0.02 |
| FEF25-75/FVC (Pre BD) | Sphingosine-1-phosphate\* | Lipid | Sphingolipids | HMDB0000277 | -1.60 | 0.05 | -2.69 | 0.003 | -2.10 | 0.0005 | 0.02 |
| FEF25-75/FVC (Pre BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 2.47 | 0.002 | 5.08 | 2.81E-08 | 3.61 | 1.79E-09 | 2.64E-07 |
| FEF25-75/FVC (Pre BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | -2.16 | 0.006 | -4.67 | 2.31E-07 | -3.25 | 4.04E-08 | 3.97E-06 |
| FEF25-75/FVC (Pre BD) | Phenylacetylglutamine\* | Peptide | Acetylated Peptides | HMDB0006344 | -1.60 | 0.04 | -2.2 | 0.02 | -1.86 | 0.002 | 0.04 |
| FEF25-75/FVC (Pre BD) | 2-Aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -2.27 | 0.005 | -2.96 | 0.001 | -2.57 | 1.63E-05 | 0.0007 |
| FEF25-75/FVC (Post BD) | Asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | -1.90 | 0.02 | -2.22 | 0.02 | -2.03 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | Aspartic acid | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000191 | 0.50 | 0.52 | 7.59 | 5.12E-15 | 3.35 | 3.25E-08 | 3.19E-06 |
| FEF25-75/FVC (Post BD) | Pyroglutamic acid\* | Amino Acid | Glutathione Metabolism | HMDB0000267 | -2.60 | 0.001 | -2.69 | 0.004 | -2.64 | 1.41E-05 | 0.0008 |
| FEF25-75/FVC (Post BD) | 2-Ketoisovaleric acid KIV\* | Amino Acid | Leucine, Isoleucine and Valine Metabolism | HMDB0000019 | 2.57 | 0.001 | 1.09 | 0.24 | 1.96 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | 2-Aminoadipic acid\* | Amino Acid | Lysine Metabolism | HMDB0000510 | -2.25 | 0.004 | -1.82 | 0.06 | -2.08 | 0.0007 | 0.02 |
| FEF25-75/FVC (Post BD) | Formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | -1.43 | 0.07 | -2.56 | 0.006 | -1.90 | 0.002 | 0.03 |
| FEF25-75/FVC (Post BD) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -1.59 | 0.05 | -6.32 | 4.60E-11 | -3.54 | 6.56E-09 | 1.29E-06 |
| FEF25-75/FVC (Post BD) | Acisoga\* | Amino Acid | Polyamine Metabolism | HMDB0061384 | -0.62 | 0.42 | -3.92 | 2.49E-05 | -1.99 | 0.0009 | 0.02 |
| FEF25-75/FVC (Post BD) | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -1.37 | 0.08 | -2.65 | 0.005 | -1.90 | 0.002 | 0.03 |
| FEF25-75/FVC (Post BD) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -1.94 | 0.02 | -4.67 | 5.39E-07 | -3.12 | 3.09E-07 | 2.02E-05 |
| FEF25-75/FVC (Post BD) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | -2.63 | 0.0008 | -6.64 | 5.13E-12 | -4.25 | 2.15E-12 | 1.27E-09 |
| FEF25-75/FVC (Post BD) | Lactic acid\* | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000190 | -2.43 | 0.003 | -1.53 | 0.10 | -2.05 | 0.0008 | 0.02 |
| FEF25-75/FVC (Post BD) | 9-Cis-retinoic acid\* | Cofactors and Vitamins | Vitamin A Metabolism | HMDB0002369 | -2.04 | 0.01 | -6.37 | 5.52E-11 | -3.78 | 5.65E-10 | 1.66E-07 |
| FEF25-75/FVC (Post BD) | Glyoxylic Acid\* | Energy | TCA Cycle | HMDB0000119 | 1.60 | 0.04 | 2.31 | 0.01 | 1.89 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | -2.75 | 0.0005 | -4.41 | 4.03E-06 | -3.42 | 1.61E-08 | 2.37E-06 |
| FEF25-75/FVC (Post BD) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -1.68 | 0.03 | -5.46 | 8.98E-09 | -3.25 | 8.77E-08 | 6.46E-06 |
| FEF25-75/FVC (Post BD) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | -1.58 | 0.05 | -2.92 | 0.002 | -2.14 | 0.0004 | 0.01 |
| FEF25-75/FVC (Post BD) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | -0.28 | 0.72 | -5.84 | 1.39E-09 | -2.51 | 3.43E-05 | 0.002 |
| FEF25-75/FVC (Post BD) | 20-Hydroxy-N-Arachidonoyl Taurine\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | Pubchem 53394637 | -1.25 | 0.11 | -3.02 | 0.001 | -1.98 | 0.0009 | 0.02 |
| FEF25-75/FVC (Post BD) | LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | -0.09 | 0.91 | -4.52 | 2.12E-06 | -1.95 | 0.002 | 0.03 |
| FEF25-75/FVC (Post BD) | Choline\* | Lipid | Phospholipid Metabolism | HMDB0000097 | -2.86 | 0.0003 | -2.34 | 0.01 | -2.64 | 1.19E-05 | 0.0007 |
| FEF25-75/FVC (Post BD) | Trimethylamine-N-oxide\* | Lipid | Phospholipid Metabolism | HMDB0000925 | -1.69 | 0.03 | -2.23 | 0.02 | -1.92 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | Taurodeoxycholic acid / Taurochenodeoxycholic acid\* | Lipid | Secondary Bile Acid Metabolism | HMDB0000896 | -2.07 | 0.01 | -2.27 | 0.02 | -2.15 | 0.0005 | 0.02 |
| FEF25-75/FVC (Post BD) | Sphingosine-1-phosphate\* | Lipid | Sphingolipids | HMDB0000277 | -1.97 | 0.02 | -2.00 | 0.03 | -1.99 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 2.37 | 0.003 | 4.59 | 1.22E-06 | 3.30 | 5.54E-08 | 4.66E-06 |
| FEF25-75/FVC (Post BD) | Xanthosine\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000299 | -2.62 | 0.0008 | -4.42 | 2.58E-06 | -3.36 | 2.06E-08 | 2.42E-06 |
| FEF25-75/FVC (Post BD) | Pseudouridine\* | Nucleotide | Pyrimidine Metabolism, Uracil containing | HMDB0000767 | -1.66 | 0.04 | -2.38 | 0.01 | -1.97 | 0.001 | 0.03 |
| FEF25-75/FVC (Post BD) | Phenylacetylglutamine\* | Peptide | Acetylated Peptides | HMDB0006344 | -1.66 | 0.03 | -2.88 | 0.002 | -2.16 | 0.0003 | 0.01 |
| FEF25-75/FVC (Post BD) | 2-Aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -1.93 | 0.01 | -3.09 | 0.0009 | -2.41 | 5.93E-05 | 0.002 |

\*refers to single-domain metabolites. Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E4: Association between Metabolites and Th2 Inflammation, adjusted for Age, Sex, BMI, Race, and ICS use (Combined Q-Value < 0.05 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **CAMP** | | **GACRS** | | **Combined** | | |
| **Clinical Marker** | **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Q-Value** |
| EOS ≥300 | 1-Methylhistamine | Amino Acid | Histidine Metabolism | HMDB0000898 | 0.39 | 1.08E-06 | 0.23 | 0.001 | 0.30 | 1.28E-08 | 2.52E-06 |
| EOS ≥300 | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 0.25 | 0.0005 | 0.37 | 1.93E-08 | 0.31 | 8.37E-11 | 2.57E-08 |
| EOS ≥300 | Formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | 0.04 | 0.57 | 0.30 | 4.16E-06 | 0.18 | 0.0002 | 0.01 |
| EOS ≥300 | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | 0.16 | 0.02 | 0.29 | 1.94E-05 | 0.23 | 2.49E-06 | 0.0004 |
| EOS ≥300 | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | 0.32 | 1.25E-05 | 0.32 | 1.62E-06 | 0.32 | 8.74E-11 | 2.57E-08 |
| EOS ≥300 | Bilirubin\* | Cofactors and Vitamins | Hemoglobin and Porphyrin Metabolism | HMDB0000054 | -0.10 | 0.15 | -0.23 | 0.0006 | -0.17 | 0.0005 | 0.02 |
| EOS ≥300 | Niacinamide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0001406 | 0.21 | 0.004 | 0.13 | 0.05 | 0.16 | 0.0007 | 0.02 |
| EOS ≥300 | 2-hydroxyoctanoate\* | Lipid | Fatty Acid Metabolism | HMDB0000711 | 0.19 | 0.005 | 0.16 | 0.01 | 0.18 | 0.0002 | 0.01 |
| EOS ≥300 | Arachidonic acid | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | -0.19 | 0.008 | -0.16 | 0.01 | -0.17 | 0.0002 | 0.01 |
| EOS ≥300 | LPC(18:2) | Lipid | Lysophospholipid | HMDB0010386 | 0.22 | 0.002 | 0.11 | 0.08 | 0.16 | 0.0008 | 0.02 |
| EOS ≥300 | LPC(20:5) | Lipid | Lysophospholipid | HMDB0010397 | 0.19 | 0.007 | 0.11 | 0.08 | 0.15 | 0.002 | 0.04 |
| EOS ≥300 | LPE(18:1)\* | Lipid | Lysophospholipid | HMDB0011506 | 0.20 | 0.004 | 0.11 | 0.10 | 0.15 | 0.002 | 0.04 |
| EOS ≥300 | LPE(18:2)\* | Lipid | Lysophospholipid | HMDB0011507 | 0.19 | 0.007 | 0.11 | 0.09 | 0.14 | 0.002 | 0.05 |
| EOS ≥300 | PC(30:1)\* | Lipid | Phosphatidylcholine | HMDB0007870 | 0.10 | 0.14 | 0.20 | 0.002 | 0.16 | 0.001 | 0.03 |
| EOS ≥300 | PC(32:2)\* | Lipid | Phosphatidylcholine | HMDB0007874 | 0.10 | 0.15 | 0.22 | 0.0009 | 0.17 | 0.0006 | 0.02 |
| EOS ≥300 | PC(34:3)\* | Lipid | Phosphatidylcholine | HMDB0008006 | 0.10 | 0.14 | 0.21 | 0.001 | 0.16 | 0.0007 | 0.02 |
| EOS ≥300 | PC(34:4)\* | Lipid | Phosphatidylcholine | HMDB0007883 | 0.10 | 0.16 | 0.19 | 0.004 | 0.15 | 0.002 | 0.04 |
| EOS ≥300 | PC(36:3)\* | Lipid | Phosphatidylcholine | HMDB0008105 | 0.13 | 0.06 | 0.22 | 0.0006 | 0.18 | 0.0001 | 0.01 |
| EOS ≥300 | PC(36:4)\_A\* | Lipid | Phosphatidylcholine | HMDB0007983 | 0.14 | 0.05 | 0.18 | 0.004 | 0.16 | 0.0006 | 0.02 |
| EOS ≥300 | PC(P-36:0)/PC(O-36:1) | Lipid | Phosphatidylcholine | HMDB0011241 | 0.13 | 0.07 | 0.23 | 0.0009 | 0.18 | 0.0003 | 0.01 |
| EOS ≥300 | PC(P-36:1)/PC(O-36:2)\* | Lipid | Phosphatidylcholine | HMDB0011243 | 0.16 | 0.03 | 0.26 | 0.0002 | 0.21 | 2.89E-05 | 0.003 |
| EOS ≥300 | PC(P-38:3)/PC(O-38:4)\* | Lipid | Phosphatidylcholine | HMDB0011252 | 0.14 | 0.05 | 0.21 | 0.002 | 0.18 | 0.0003 | 0.02 |
| EOS ≥300 | PC(P-38:5)/PC(O-38:6)\* | Lipid | Phosphatidylcholine | HMDB0011319 | 0.19 | 0.005 | 0.16 | 0.01 | 0.18 | 0.0002 | 0.01 |
| EOS ≥300 | PE(38:6)\* | Lipid | Phosphatidylethanolamine | HMDB0009102 | -0.14 | 0.05 | -0.19 | 0.004 | -0.16 | 0.0006 | 0.02 |
| EOS ≥300 | PE(P-44:12)/PE(O-44:13) | Lipid | Phosphatidylethanolamine |  | 0.13 | 0.06 | 0.19 | 0.004 | 0.16 | 0.0007 | 0.02 |
| EOS ≥300 | Metronidazole\* | Xenobiotics | Drug | HMDB0015052 | 0.14 | 0.05 | 0.18 | 0.004 | 0.16 | 0.0006 | 0.02 |
| Log10(EOS) | 1-Methylhistamine | Amino Acid | Histidine Metabolism | HMDB0000898 | 0.11 | 1.50E-10 | 0.05 | 0.0001 | 0.07 | 3.51E-12 | 1.03E-09 |
| Log10(EOS) | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 0.06 | 0.0001 | 0.09 | 2.67E-12 | 0.08 | 1.74E-15 | 1.02E-12 |
| Log10(EOS) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | 0.05 | 0.003 | 0.08 | 4.65E-09 | 0.07 | 7.55E-11 | 1.48E-08 |
| Log10(EOS) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | 0.05 | 0.003 | 0.06 | 5.51E-07 | 0.06 | 5.88E-09 | 8.66E-07 |
| Log10(EOS) | Tryptophan | Amino Acid | Tryptophan Metabolism | HMDB0000929 | 0.04 | 0.01 | 0.03 | 0.03 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | Glyceric acid | Carbohydrate | Glycolysis, Gluconeogenesis, and Pyruvate Metabolism | HMDB0000139 | 0.01 | 0.98 | 0.05 | 5.19E-05 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | Bilirubin\* | Cofactors and Vitamins | Hemoglobin and Porphyrin Metabolism | HMDB0000054 | -0.05 | 0.005 | -0.05 | 8.27E-05 | -0.05 | 1.33E-06 | 0.0002 |
| Log10(EOS) | Biliverdin\* | Cofactors and Vitamins | Hemoglobin and Porphyrin Metabolism | HMDB0001008 | -0.06 | 0.0004 | -0.02 | 0.05 | -0.04 | 0.0002 | 0.006 |
| Log10(EOS) | Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | 0.04 | 0.03 | 0.02 | 0.06 | 0.03 | 0.005 | 0.05 |
| Log10(EOS) | Niacinamide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0001406 | 0.05 | 0.004 | 0.03 | 0.007 | 0.04 | 0.0001 | 0.003 |
| Log10(EOS) | ADP\* | Energy | TCA Cycle | HMDB0001341 | 0.04 | 0.02 | 0.02 | 0.05 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | ATP\* | Energy | TCA Cycle | HMDB0000538 | 0.03 | 0.06 | 0.03 | 0.02 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | C16 carnitine\* | Lipid | Carnitine Metabolism | HMDB0000222 | -0.04 | 0.009 | -0.02 | 0.08 | -0.03 | 0.003 | 0.03 |
| Log10(EOS) | C18:1 carnitine | Lipid | Carnitine Metabolism | HMDB0005065 | -0.04 | 0.009 | -0.02 | 0.08 | -0.03 | 0.003 | 0.03 |
| Log10(EOS) | C18:2 carnitine\* | Lipid | Carnitine Metabolism | HMDB0006469 | -0.04 | 0.02 | -0.03 | 0.04 | -0.03 | 0.002 | 0.03 |
| Log10(EOS) | C20:4 carnitine | Lipid | Carnitine Metabolism | HMDB0006455 | -0.03 | 0.11 | -0.03 | 0.01 | -0.03 | 0.003 | 0.03 |
| Log10(EOS) | DG(36:0)\* | Lipid | Diacylglycerol | HMDB0007158 | 0.01 | 0.49 | 0.04 | 0.0008 | 0.03 | 0.002 | 0.03 |
| Log10(EOS) | 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | 0.01 | 0.42 | 0.05 | 2.55E-05 | 0.04 | 0.0001 | 0.003 |
| Log10(EOS) | 2-Aminooctanoate\* | Lipid | Fatty Acid Metabolism | HMDB0000991 | 0.01 | 0.38 | 0.04 | 0.002 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | 2-Hydroxyoctanoate\* | Lipid | Fatty Acid Metabolism | HMDB0000711 | 0.05 | 0.002 | 0.03 | 0.005 | 0.04 | 3.88E-05 | 0.002 |
| Log10(EOS) | 3-Methyladipate | Lipid | Fatty Acid Metabolism | HMDB0000555 | 0.01 | 0.51 | 0.04 | 0.001 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | 0.03 | 0.05 | 0.05 | 0.0003 | 0.04 | 3.68E-05 | 0.002 |
| Log10(EOS) | Azelate | Lipid | Fatty Acid Metabolism | HMDB0000784 | 0.02 | 0.35 | 0.06 | 7.28E-07 | 0.05 | 5.63E-06 | 0.0005 |
| Log10(EOS) | Sebacate | Lipid | Fatty Acid Metabolism | HMDB0000792 | 0.01 | 0.87 | 0.06 | 4.49E-06 | 0.04 | 0.0002 | 0.005 |
| Log10(EOS) | 13-HODE\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0004667 | 0.03 | 0.11 | 0.04 | 0.004 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | LPC(18:2) | Lipid | Lysophospholipid | HMDB0010386 | 0.07 | 0.0001 | 0.02 | 0.14 | 0.04 | 0.0005 | 0.01 |
| Log10(EOS) | LPC(20:5) | Lipid | Lysophospholipid | HMDB0010397 | 0.06 | 0.0006 | 0.03 | 0.04 | 0.04 | 0.0002 | 0.006 |
| Log10(EOS) | LPC(22:6)\* | Lipid | Lysophospholipid | HMDB0010404 | 0.05 | 0.007 | 0.02 | 0.10 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | LPE(18:1)\* | Lipid | Lysophospholipid | HMDB0011506 | 0.07 | 7.08E-05 | 0.02 | 0.21 | 0.03 | 0.0007 | 0.01 |
| Log10(EOS) | LPE(18:2)\* | Lipid | Lysophospholipid | HMDB0011507 | 0.06 | 0.0003 | 0.01 | 0.26 | 0.03 | 0.002 | 0.03 |
| Log10(EOS) | LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | 0.01 | 0.41 | 0.04 | 0.005 | 0.03 | 0.005 | 0.05 |
| Log10(EOS) | PC(34:3)\* | Lipid | Phosphatidylcholine | HMDB0008006 | 0.03 | 0.13 | 0.04 | 0.005 | 0.03 | 0.002 | 0.02 |
| Log10(EOS) | PC(36:0)\* | Lipid | Phosphatidylcholine | HMDB0008036 | 0.03 | 0.11 | 0.04 | 0.004 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | PC(36:1)\* | Lipid | Phosphatidylcholine | HMDB0008038 | 0.03 | 0.11 | 0.04 | 0.002 | 0.04 | 0.0005 | 0.01 |
| Log10(EOS) | PC(36:2)\* | Lipid | Phosphatidylcholine | HMDB0008039 | 0.05 | 0.004 | 0.03 | 0.02 | 0.04 | 0.0003 | 0.008 |
| Log10(EOS) | PC(36:3)\* | Lipid | Phosphatidylcholine | HMDB0008105 | 0.05 | 0.003 | 0.04 | 0.001 | 0.04 | 1.26E-05 | 0.0008 |
| Log10(EOS) | PC(36:4)\_A\* | Lipid | Phosphatidylcholine | HMDB0007983 | 0.06 | 0.0006 | 0.03 | 0.01 | 0.04 | 3.96E-05 | 0.002 |
| Log10(EOS) | PC(38:2)\* | Lipid | Phosphatidylcholine | HMDB0008270 | 0.04 | 0.03 | 0.03 | 0.02 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | PC(38:3)\* | Lipid | Phosphatidylcholine | HMDB0008047 | 0.03 | 0.07 | 0.03 | 0.04 | 0.03 | 0.006 | 0.05 |
| Log10(EOS) | PC(P-34:2)/PC(O-34:3)\* | Lipid | Phosphatidylcholine | HMDB0011211 | 0.01 | 0.38 | 0.04 | 0.002 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | PC(P-36:0)/PC(O-36:1) | Lipid | Phosphatidylcholine | HMDB0011241 | 0.04 | 0.04 | 0.04 | 0.004 | 0.04 | 0.0004 | 0.008 |
| Log10(EOS) | PC(P-36:1)/PC(O-36:2)\* | Lipid | Phosphatidylcholine | HMDB0011243 | 0.05 | 0.006 | 0.05 | 0.0005 | 0.05 | 7.82E-06 | 0.0006 |
| Log10(EOS) | PC(P-38:3)/PC(O-38:4)\* | Lipid | Phosphatidylcholine | HMDB0011252 | 0.03 | 0.05 | 0.04 | 0.004 | 0.04 | 0.0005 | 0.01 |
| Log10(EOS) | PC(P-38:5)/PC(O-38:6)\* | Lipid | Phosphatidylcholine | HMDB0011319 | 0.05 | 0.002 | 0.03 | 0.005 | 0.04 | 3.88E-05 | 0.002 |
| Log10(EOS) | PE(36:3)\* | Lipid | Phosphatidylethanolamine | HMDB0009060 | 0.06 | 0.0008 | 0.01 | 0.26 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | PE(38:6)\* | Lipid | Phosphatidylethanolamine | HMDB0009102 | -0.02 | 0.30 | -0.04 | 0.0004 | -0.03 | 0.0006 | 0.01 |
| Log10(EOS) | PE(P-36:0)/PE(O-36:1)\* | Lipid | Phosphatidylethanolamine | HMDB0009016 | 0.03 | 0.08 | 0.04 | 0.002 | 0.04 | 0.0004 | 0.008 |
| Log10(EOS) | PE(P-36:2)/PE(O-36:3)\* | Lipid | Phosphatidylethanolamine | HMDB0011441 | 0.03 | 0.12 | 0.03 | 0.02 | 0.03 | 0.006 | 0.05 |
| Log10(EOS) | PE(P-36:3)/PE(O-36:4) | Lipid | Phosphatidylethanolamine | HMDB0011442 | 0.03 | 0.11 | 0.03 | 0.008 | 0.03 | 0.002 | 0.03 |
| Log10(EOS) | PE(P-38:2)/PE(O-38:3)\* | Lipid | Phosphatidylethanolamine | HMDB0011384 | 0.01 | 0.38 | 0.04 | 0.002 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | PE(P-38:5)/PE(O-38:6)\* | Lipid | Phosphatidylethanolamine | HMDB0011387 | 0.03 | 0.15 | 0.03 | 0.01 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | PE(P-44:12)/PE(O-44:13) | Lipid | Phosphatidylethanolamine |  | 0.06 | 0.0005 | 0.03 | 0.01 | 0.04 | 5.65E-05 | 0.002 |
| Log10(EOS) | Tauro-alpha-muricholate/tauro-beta-muricholate\* | Lipid | Primary Bile Acid Metabolism | HMDB0000932 | 0.04 | 0.01 | 0.03 | 0.03 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | TG(52:2)\* | Lipid | Triacylglycerol | HMDB0005369 | 0.03 | 0.05 | 0.03 | 0.04 | 0.03 | 0.004 | 0.04 |
| Log10(EOS) | TG(54:2)\* | Lipid | Triacylglycerol | HMDB0005403 | 0.04 | 0.02 | 0.02 | 0.06 | 0.03 | 0.004 | 0.03 |
| Log10(EOS) | TG(54:3)\* | Lipid | Triacylglycerol | HMDB0005405 | 0.04 | 0.03 | 0.03 | 0.04 | 0.03 | 0.004 | 0.03 |
| Log10(EOS) | TG(55:2)\* | Lipid | Triacylglycerol | HMDB0042226 | 0.04 | 0.01 | 0.03 | 0.03 | 0.03 | 0.001 | 0.02 |
| Log10(EOS) | TG(55:3)\* | Lipid | Triacylglycerol | HMDB0042466 | 0.04 | 0.03 | 0.02 | 0.07 | 0.03 | 0.006 | 0.05 |
| Log10(EOS) | TG(56:1)\* | Lipid | Triacylglycerol | HMDB0005396 | 0.06 | 0.0009 | 0.02 | 0.16 | 0.03 | 0.002 | 0.03 |
| Log10(EOS) | TG(56:2)\* | Lipid | Triacylglycerol | HMDB0005404 | 0.05 | 0.007 | 0.02 | 0.10 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | TG(56:3)\* | Lipid | Triacylglycerol | HMDB0005410 | 0.04 | 0.01 | 0.02 | 0.09 | 0.03 | 0.004 | 0.04 |
| Log10(EOS) | Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | -0.04 | 0.02 | -0.05 | 0.0003 | -0.04 | 1.57E-05 | 0.0009 |
| Log10(EOS) | Adenine | Nucleotide | Purine Metabolism, Adenine containing | HMDB0000034 | 0.02 | 0.33 | 0.04 | 0.003 | 0.03 | 0.003 | 0.03 |
| Log10(EOS) | 2-Aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | 0.05 | 0.004 | 0.02 | 0.15 | 0.03 | 0.004 | 0.03 |
| Log10(EOS) | Metronidazole\* | Xenobiotics | Drug | HMDB0015052 | 0.06 | 0.0006 | 0.03 | 0.01 | 0.04 | 3.96E-05 | 0.002 |

\*refers to single-domain metabolites. Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E5: Association between Metabolites and non-Th2 Inflammation, adjusted for Age, Sex, BMI, Race, and ICS use (Combined Q-Value < 0.05 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **CAMP** | | **GACRS** | | **Combined** | | |
| **Clinical Marker** | **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Coef.** | **P-Value** | **Q-Value** |
| Log10(NEU) | Alanine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000161 | -0.02 | 0.01 | -0.14 | 0.002 | -0.02 | 0.003 | 0.04 |
| Log10(NEU) | N-Acetyl-L-Aspartic acid\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000812 | -0.02 | 0.002 | -0.06 | 0.18 | -0.02 | 0.001 | 0.02 |
| Log10(NEU) | Glycine | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000123 | -0.03 | 3.30E-05 | -0.09 | 0.09 | -0.03 | 1.35E-05 | 0.0008 |
| Log10(NEU) | Serine\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000187 | -0.02 | 0.003 | -0.05 | 0.33 | -0.02 | 0.002 | 0.03 |
| Log10(NEU) | Threonine\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000167 | -0.03 | 3.57E-05 | -0.08 | 0.08 | -0.03 | 1.39E-05 | 0.0008 |
| Log10(NEU) | Anserine\* | Amino Acid | Histidine Metabolism | HMDB0000194 | 0.02 | 0.0005 | 0.03 | 0.48 | 0.02 | 0.0004 | 0.01 |
| Log10(NEU) | Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | 0.02 | 0.0007 | 0.05 | 0.31 | 0.02 | 0.0005 | 0.01 |
| Log10(NEU) | Diacetylspermine | Amino Acid | Polyamine Metabolism | HMDB0002172 | 0.02 | 0.0003 | 0.21 | 1.69E-06 | 0.03 | 1.68E-05 | 0.0009 |
| Log10(NEU) | Indole-3-carboxylic acid\* | Amino Acid | Tryptophan Metabolism | HMDB0003320 | -0.02 | 0.002 | -0.01 | 0.74 | -0.02 | 0.001 | 0.02 |
| Log10(NEU) | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -0.02 | 0.001 | -0.14 | 0.002 | -0.02 | 0.0003 | 0.01 |
| Log10(NEU) | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.03 | 1.69E-05 | -0.03 | 0.46 | -0.03 | 1.15E-05 | 0.0008 |
| Log10(NEU) | Arginine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000517 | -0.02 | 0.006 | -0.04 | 0.41 | -0.02 | 0.004 | 0.05 |
| Log10(NEU) | Citrulline\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000904 | -0.02 | 0.007 | -0.13 | 0.004 | -0.02 | 0.002 | 0.03 |
| Log10(NEU) | Hydroxyproline | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000725 | -0.02 | 0.0002 | -0.11 | 0.02 | -0.03 | 6.38E-05 | 0.003 |
| Log10(NEU) | N-acetylornithine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0003357 | 0.02 | 0.0009 | 0.01 | 0.92 | 0.02 | 0.0009 | 0.02 |
| Log10(NEU) | 2-Hydroxybutyric acid\* | Energy | TCA Cycle | HMDB0000008 | 0.03 | 4.27E-05 | 0.10 | 0.03 | 0.03 | 1.30E-05 | 0.0008 |
| Log10(NEU) | Succinic acid/Methylmalonic acid\* | Energy | TCA Cycle | HMDB0000254 | 0.02 | 0.002 | 0.06 | 0.14 | 0.02 | 0.001 | 0.02 |
| Log10(NEU) | C4-OH carnitine\* | Lipid | Carnitine Metabolism | HMDB0013127 | 0.02 | 0.001 | 0.14 | 0.004 | 0.02 | 0.0003 | 0.01 |
| Log10(NEU) | Cer(d18:1/16:0)\* | Lipid | Ceramides | HMDB0004949 | 0.02 | 0.0001 | 0.05 | 0.28 | 0.02 | 6.23E-05 | 0.003 |
| Log10(NEU) | 16-Hydroxypalmitate\* | Lipid | Fatty Acid Metabolism | HMDB0006294 | 0.02 | 0.001 | 0.11 | 0.01 | 0.02 | 0.0005 | 0.01 |
| Log10(NEU) | 3-Hydroxydecanoate\* | Lipid | Fatty Acid Metabolism | HMDB0002203 | 0.02 | 0.002 | 0.01 | 0.75 | 0.02 | 0.001 | 0.02 |
| Log10(NEU) | Hexadecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000672 | 0.02 | 0.001 | 0.10 | 0.03 | 0.02 | 0.0004 | 0.01 |
| Log10(NEU) | Tetradecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000872 | 0.02 | 8.98E-05 | 0.05 | 0.30 | 0.02 | 5.39E-05 | 0.002 |
| Log10(NEU) | Nervonic acid\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0002368 | 0.03 | 3.39E-06 | 0.13 | 0.003 | 0.03 | 5.27E-07 | 0.0003 |
| Log10(NEU) | Oleoyl Leucine\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0028933 | 0.02 | 0.0006 | 0.02 | 0.62 | 0.02 | 0.0005 | 0.01 |
| Log10(NEU) | LPC(20:5) | Lipid | Lysophospholipid | HMDB0010397 | 0.02 | 0.004 | 0.05 | 0.25 | 0.02 | 0.003 | 0.03 |
| Log10(NEU) | PC(32:0)\* | Lipid | Phosphatidylcholine | HMDB0007871 | 0.02 | 0.006 | 0.07 | 0.15 | 0.02 | 0.003 | 0.04 |
| Log10(NEU) | PC(P-36:0)/PC(O-36:1) | Lipid | Phosphatidylcholine | HMDB0011241 | 0.02 | 0.003 | 0.05 | 0.33 | 0.02 | 0.002 | 0.03 |
| Log10(NEU) | PE(36:1)\* | Lipid | Phosphatidylethanolamine | HMDB0008993 | 0.02 | 0.002 | 0.01 | 1.00 | 0.02 | 0.007 | 0.03 |
| Log10(NEU) | CE(18:0)\* | Lipid | Sterol | HMDB0010368 | -0.02 | 0.005 | -0.06 | 0.20 | -0.02 | 0.003 | 0.04 |
| Log10(NEU) | TG(54:9)\* | Lipid | Triacylglycerol | HMDB0010498 | 0.02 | 0.006 | 0.05 | 0.35 | 0.02 | 0.004 | 0.05 |
| NEU% | Alanine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000161 | -1.19 | 0.0007 | -2.72 | 0.0004 | -1.45 | 5.00E-06 | 0.0006 |
| NEU% | Glycine | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000123 | -1.43 | 9.57E-05 | -2.18 | 0.008 | -1.55 | 3.26E-06 | 0.0005 |
| NEU% | Threonine\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000167 | -1.37 | 9.71E-05 | -1.42 | 0.06 | -1.38 | 1.40E-05 | 0.001 |
| NEU% | Histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | -0.51 | 0.14 | -3.43 | 5.18E-06 | -1.03 | 0.001 | 0.03 |
| NEU% | Histidine\* | Amino Acid | Histidine Metabolism | HMDB0000177 | -0.76 | 0.03 | -2.64 | 0.0004 | -1.11 | 0.0005 | 0.02 |
| NEU% | Diacetylspermine | Amino Acid | Polyamine Metabolism | HMDB0002172 | 0.94 | 0.01 | 4.58 | 2.39E-10 | 1.73 | 1.83E-07 | 0.0001 |
| NEU% | Kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -1.01 | 0.004 | -2.41 | 0.001 | -1.27 | 5.95E-05 | 0.004 |
| NEU% | Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -1.63 | 5.59E-06 | -0.17 | 0.83 | -1.36 | 2.32E-05 | 0.002 |
| NEU% | Xanthurenic acid\* | Amino Acid | Tryptophan Metabolism | HMDB0000881 | -0.79 | 0.03 | -2.8 | 0.0002 | -1.16 | 0.0003 | 0.01 |
| NEU% | Hydroxyproline | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000725 | -1.64 | 8.18E-06 | -1.66 | 0.03 | -1.64 | 7.04E-07 | 0.0002 |
| NEU% | Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -0.96 | 0.006 | -1.37 | 0.08 | -1.03 | 0.001 | 0.04 |
| NEU% | Niacinamide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0001406 | -1.19 | 0.0007 | -1.09 | 0.16 | -1.17 | 0.0003 | 0.01 |
| NEU% | 2-Hydroxybutyric acid\* | Energy | TCA Cycle | HMDB0000008 | 1.32 | 0.0002 | 2.59 | 0.0005 | 1.56 | 1.24E-06 | 0.0002 |
| NEU% | C4-OH carnitine\* | Lipid | Carnitine Metabolism | HMDB0013127 | 0.69 | 0.05 | 2.96 | 0.0001 | 1.08 | 0.0006 | 0.02 |
| NEU% | Tetradecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000872 | 1.06 | 0.003 | 1.06 | 0.15 | 1.06 | 0.0009 | 0.03 |
| NEU% | Myristoleic acid\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0002000 | 0.88 | 0.01 | 1.78 | 0.02 | 1.04 | 0.0009 | 0.03 |
| NEU% | N-Oleoyl Taurine | Lipid | Long Chain Monounsaturated Fatty Acid | CAS:52514-04-2 | 1.08 | 0.002 | 0.71 | 0.34362696 | 1.01 | 0.001 | 0.04 |
| NEU% | Nervonic acid\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0002368 | 0.98 | 0.004 | 2.87 | 0.00011544 | 1.32 | 2.45E-05 | 0.002 |
| NEU% | Oleoyl Leucine\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0028933 | 1.35 | 0.0001 | 0.39 | 0.60260862 | 1.18 | 0.0002 | 0.009 |
| NEU% | N-Palmitoyl Taurine | Lipid | Long Chain Saturated Fatty Acid | CAS:83982-06-3 | 1.22 | 0.0005 | 1.07 | 0.15330807 | 1.19 | 0.0002 | 0.009 |
| NEU% | LPC(18:2) | Lipid | Lysophospholipid | HMDB0010386 | -0.35 | 0.33 | -4.00 | 1.41E-07 | -1.03 | 0.002 | 0.04 |
| NEU% | PE(P-44:12)/PE(O-44:13) | Lipid | Phosphatidylethanolamine |  | -0.26 | 0.47 | -4.32 | 1.26E-08 | -1.00 | 0.002 | 0.05 |

\*refers to single-domain metabolites\*refers to single-domain metabolites. Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E6: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for Airway Hyperresponsiveness**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| Aspartic acid | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000191 | -3.17 |
| Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -2.66 |
| IMP\* | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0011681 | -1.50 |
| Hippuric acid\* | Xenobiotics | Benzoate Metabolism | HMDB0000714 | 0.60 |
| N-Oleoyl Dopamine\* | Lipid | Endocannabinoid | CAS:105955-11-1 | 0.80 |

\*refers to single-domain metabolites

**Table E7: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for Atopy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -0.95 |
| histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 1.84 |

\*refers to single-domain metabolites

**Table E8: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for Lung Function (Absolute)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| SM(d18:1/16:1)\* | Lipid | Sphingolipids | HMDB0029216 | -8.66 |
| indoleacetate\* | Amino Acid | Tryptophan Metabolism | HMDB0000197 | -8.66 |
| cortisol\* | Lipid | Corticosteroids | HMDB0000063 | -8.66 |
| N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | -5.92 |
| Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -4.74 |
| thiamine\* | Cofactors and Vitamins | Vitamin B1 Metabolism | HMDB0000235 | -4.61 |
| Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -4.30 |
| Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -3.24 |
| Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | -1.39 |
| 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -1.26 |
| dodecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000623 | -1.08 |
| DMGV\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0240212 | -1.08 |
| hydroxymyristate\* | Lipid | Fatty Acid Metabolism | HMDB0002261 | -0.19 |
| GABA\* | Amino Acid | Glutamate Metabolism | HMDB0000112 | -0.19 |
| N-Oleoyl Taurine | Lipid | Long Chain Monounsaturated Fatty Acid | CAS:52514-04-2 | -0.16 |
| acetyl-galactosamine\* | Carbohydrate | Aminosugar Metabolism | HMDB0000853 | -0.10 |
| Cholic acid\* | Lipid | Primary Bile Acid Metabolism | HMDB0000619 | 1.60 |
| 9.10-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004704 | 1.64 |
| asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | 2.80 |
| LPC(18:3) | Lipid | Lysophospholipid | HMDB0010387 | 3.27 |
| C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | 3.69 |
| Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 3.76 |
| C18 carnitine\* | Lipid | Carnitine Metabolism | HMDB0000848 | 5.41 |
| creatinine\* | Amino Acid | Creatine Metabolism | HMDB0000562 | 5.72 |

\*refers to single-domain metabolites

**Table E9: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for Lung Function (Ratio)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | -6.25 |
| C5:1 carnitine\* | Lipid | Carnitine Metabolism | HMDB0002366 | -5.22 |
| 12.13-diHOME | Lipid | Fatty Acid Metabolism | HMDB0004705 | -5.02 |
| Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -4.07 |
| choline\* | Lipid | Phospholipid Metabolism | HMDB0000097 | -3.17 |
| asparagine\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000168 | -2.72 |
| 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -2.63 |
| acisoga\* | Amino Acid | Polyamine Metabolism | HMDB0061384 | -1.71 |
| trimethylamine-N-oxide\* | Lipid | Phospholipid Metabolism | HMDB0000925 | -1.58 |
| Taurodeoxycholic acid / Taurochenodeoxycholic acid\* | Lipid | Secondary Bile Acid Metabolism | HMDB0000896 | -0.90 |
| phenylacetylglutamine\* | Peptide | Acetylated Peptides | HMDB0006344 | -0.78 |
| formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | -0.52 |
| LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | -0.50 |
| 20-Hydroxy-N-Arachidonoyl Taurine\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | Pubchem 53394637 | 0.25 |
| 2-Aminoadipic acid\* | Amino Acid | Lysine Metabolism | HMDB0000510 | 1.35 |
| diacetylspermine | Amino Acid | Polyamine Metabolism | HMDB0002172 | 1.50 |
| PC(36:4-OH)\* | Lipid | Phosphatidylcholine |  | 1.51 |
| N4-acetylcytidine\* | Nucleotide | Pyrimidine Metabolism, Cytidine containing | HMDB0005923 | 1.53 |
| N-Acetyl-L-Glutamine | Amino Acid | Glutamate Metabolism | HMDB0006029 | 1.53 |
| Hydroxyproline | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000725 | 1.68 |
| PE(P-36:3)/PE(O-36:4) | Lipid | Phosphatidylethanolamine | HMDB0011442 | 1.69 |
| sulfamethoxazole\* | Xenobiotics | Drug | HMDB0015150 | 3.40 |
| Phosphocreatine | Amino Acid | Creatine Metabolism | HMDB0001511 | 4.44 |
| Arachidonic acid | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | 4.74 |
| Stearic acid\* | Lipid | Long Chain Saturated Fatty Acid | HMDB0000827 | 4.94 |
| 2-ketoisovaleric acid KIV\* | Amino Acid | Leucine, Isoleucine and Valine Metabolism | HMDB0000019 | 6.99 |
| Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000289 | 10.38 |

\*refers to single-domain metabolites

**Table E10: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for Th2 Inflammation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| Bilirubin\* | Cofactors and Vitamins | Hemoglobin and Porphyrin Metabolism | HMDB0000054 | -5.00 |
| PE(38:6)\* | Lipid | Phosphatidylethanolamine | HMDB0009102 | -4.43 |
| Arachidonic acid | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0001043 | -3.19 |
| C18:2 carnitine\* | Lipid | Carnitine Metabolism | HMDB0006469 | -2.69 |
| TG(55:3)\* | Lipid | Triacylglycerol | HMDB0042466 | -0.43 |
| Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -0.41 |
| LPE(20:1) | Lipid | Lysophospholipid | HMDB0011512 | -0.39 |
| ADP\* | Energy | TCA Cycle | HMDB0001341 | -0.38 |
| 2-aminohippuric acid | Xenobiotics | Benzoate Metabolism | HMDB0001867 | -0.38 |
| Adenine | Nucleotide | Purine Metabolism, Adenine containing | HMDB0000034 | -0.36 |
| 3-methyladipate | Lipid | Fatty Acid Metabolism | HMDB0000555 | -0.35 |
| DG(36:0)\* | Lipid | Diacylglycerol | HMDB0007158 | -0.31 |
| tauro-alpha-muricholate/tauro-beta-muricholate\* | Lipid | Primary Bile Acid Metabolism | HMDB0000932 | -0.24 |
| tryptophan\* | Amino Acid | Tryptophan Metabolism | HMDB0000929 | -0.24 |
| 13-HODE\* | Lipid | Long Chain Polyunsaturated Fatty Acid (n3 and n6) | HMDB0004667 | -0.24 |
| formylmethionine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0001015 | 0.18 |
| PC(34:3)\* | Lipid | Phosphatidylcholine | HMDB0008006 | 1.29 |
| LPC(18:2) | Lipid | Lysophospholipid | HMDB0010386 | 1.44 |
| metronidazole\* | Xenobiotics | Drug | HMDB0015052 | 1.64 |
| 2-hydroxyoctanoate\* | Lipid | Fatty Acid Metabolism | HMDB0000711 | 1.77 |
| PC(P-36:1)/PC(O-36:2)\* | Lipid | Phosphatidylcholine | HMDB0011243 | 2.33 |
| Taurine | Amino Acid | Methionine, Cysteine, SAM and Taurine Metabolism | HMDB0000251 | 3.23 |
| Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | 3.81 |
| histamine | Amino Acid | Histidine Metabolism | HMDB0000870 | 4.52 |

\*refers to single-domain metabolites

**Table E11: Weights of Metabolites Used in the Metabolomic Risk Score (MRS) for non-Th2 Inflammation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Weight** |
| glycine | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000123 | -3.19 |
| hydroxyproline | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000725 | -3.17 |
| Kynurenine | Amino Acid | Tryptophan Metabolism | HMDB0000684 | -2.96 |
| threonine\* | Amino Acid | Glycine, Serine and Threonine Metabolism | HMDB0000167 | -2.94 |
| kynurenic acid | Amino Acid | Tryptophan Metabolism | HMDB0000715 | -2.57 |
| niacinamide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0001406 | -1.32 |
| histidine\* | Amino Acid | Histidine Metabolism | HMDB0000177 | -1.26 |
| Nudifloramide | Cofactors and Vitamins | Nicotinate and Nicotinamide Metabolism | HMDB0004193 | -1.17 |
| LPC(18:2) | Lipid | Lysophospholipid | HMDB0010386 | -1.17 |
| N-Acetyl-L-Aspartic acid\* | Amino Acid | Alanine and Aspartate Metabolism | HMDB0000812 | -1.12 |
| Citrulline\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000904 | -1.10 |
| Indole-3-carboxylic acid\* | Amino Acid | Tryptophan Metabolism | HMDB0003320 | -1.08 |
| CE(18:0)\* | Lipid | Sterol | HMDB0010368 | -1.00 |
| arginine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0000517 | -0.99 |
| LPC(20:5) | Lipid | Lysophospholipid | HMDB0010397 | 0.92 |
| PE(36:1)\* | Lipid | Phosphatidylethanolamine | HMDB0008993 | 0.92 |
| PC(P-36:0)/PC(O-36:1) | Lipid | Phosphatidylcholine | HMDB0011241 | 0.96 |
| N-acetylornithine\* | Amino Acid | Urea cycle; Arginine and Proline Metabolism | HMDB0003357 | 1.01 |
| myristoleic acid\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0002000 | 1.05 |
| anserine\* | Amino Acid | Histidine Metabolism | HMDB0000194 | 1.06 |
| Oleoyl Leucine\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0028933 | 2.31 |
| tetradecanedioate\* | Lipid | Fatty Acid Metabolism | HMDB0000872 | 2.38 |
| nervonic acid\* | Lipid | Long Chain Monounsaturated Fatty Acid | HMDB0002368 | 2.93 |
| 2-Hydroxybutyric acid\* | Energy | TCA Cycle | HMDB0000008 | 3.02 |
| diacetylspermine | Amino Acid | Polyamine Metabolism | HMDB0002172 | 3.27 |

\*refers to single-domain metabolites

**Table E12: Association between Metabolomic Risk Score (MRS) and Any Emergency Room Visits or Hospitalizations in the Previous Year, adjusted for Age, Sex, BMI, Race, and ICS use, with height included for lung function MRS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CAMP** | | **GACRS** | |
| **Metabolomic Risk Score** | **Coef.** | **P-Value** | **Coef.** | **P-Value** |
| Airway Hyperresponsiveness | -0.05 | 0.0499 | -0.04 | 0.0517 |
| Atopy | 0.006 | 0.92 | 0.04 | 0.33 |
| Lung Function (Absolute) | -0.01 | 0.0453 | -0.002 | 0.65 |
| Lung Function (Ratio) | -0.01 | 0.0415 | -0.009 | 0.0531 |
| Th2 Inflammation | 0.006 | 0.56 | -0.002 | 0.82 |
| Non-Th2 Inflammation | 0.01 | 0.27 | 0.0009 | 0.91 |

Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E13: Association between Metabolomic Risk Score (MRS) and Positive Bronchodilator Response, adjusted for Age, Sex, BMI, Race, and ICS use, with height included for lung function MRS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CAMP** | | **GACRS** | |
| **Metabolomic Risk Score** | **Coef.** | **P-Value** | **Coef.** | **P-Value** |
| Airway Hyperresponsiveness | -0.03 | 0.0488 | 0.007 | 0.74 |
| Atopy | -0.05 | 0.25 | 0.02 | 0.67 |
| Lung Function (Absolute) | 0.01 | 0.0103 | -0.005 | 0.26 |
| Lung Function (Ratio) | -0.003 | 0.40 | -0.01 | 0.0094 |
| Th2 Inflammation | -0.01 | 0.0387 | 0.001 | 0.88 |
| Non-Th2 Inflammation | -0.002 | 0.82 | 0.02 | 0.0304 |

Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E14: Association between Metabolites and Any Emergency Room Visits or Hospitalizations in the Previous Year, adjusted for Age, Sex, BMI, Race, and ICS use (Combined P-Value < 0.01 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **CAMP** | | | **GACRS** | | | **Combined** | | |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Q-Value** | **Coef.** | **P-Value** | **Q-Value** | **Coef.** | **P-Value** | **Q-Value** |
| pregnenolone sulfate | Lipid | Pregnenolone Steroids | HMDB0000774 | -0.17 | 0.13 | 0.64 | -0.28 | 0.002 | 0.93 | -0.23 | 9.20E-04 | 0.54 |
| 5-acetylamino-6-amino-3-methyluracil | Xenobiotics | Xanthine Metabolism | HMDB0004400 | 0.21 | 0.10 | 0.62 | 0.17 | 0.03 | 0.93 | 0.18 | 0.006 | 0.86 |
| cotinine | Xenobiotics | Tobacco Metabolite | HMDB0001046 | 0.30 | 0.008 | 0.50 | 0.11 | 0.17 | 0.93 | 0.17 | 0.008 | 0.86 |
| dimethylurate | Xenobiotics | Xanthine Metabolism | HMDB0001857 | 0.23 | 0.05 | 0.53 | 0.15 | 0.06 | 0.93 | 0.17 | 0.008 | 0.86 |
| levulinate | Carbohydrate | Disaccharides and Oligosaccharides | HMDB0000720 | -0.24 | 0.03 | 0.50 | -0.13 | 0.10 | 0.93 | -0.17 | 0.009 | 0.86 |

Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.

**Table E15: Association between Metabolites and Positive Bronchodilator Response, adjusted for Age, Sex, BMI, Race, and ICS use (Combined P-Value < 0.01 and Consistent Direction of Effect in CAMP and GACRS)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **CAMP** | | | **GACRS** | | | **Combined** | | |
| **Name** | **Super Pathway** | **Sub Pathway** | **HMDB** | **Coef.** | **P-Value** | **Q-Value** | **Coef.** | **P-Value** | **Q-Value** | **Coef.** | **P-Value** | **Q-Value** |
| Uric acid | Nucleotide | Purine Metabolism, (Hypo)Xanthine/Inosine containing | HMDB0000774 | -0.20 | 0.008 | 0.40 | -0.22 | 0.02 | 0.57 | -0.21 | 3.79E-04 | 0.22 |
| levulinate | Carbohydrate | Disaccharides and Oligosaccharides | HMDB0004400 | -0.18 | 0.02 | 0.49 | -0.2 | 0.03 | 0.64 | -0.19 | 0.001 | 0.26 |
| histamine | Amino Acid | Histidine Metabolism | HMDB0001046 | 0.27 | 0.001 | 0.26 | 0.12 | 0.18 | 0.89 | 0.20 | 0.001 | 0.26 |

Definition of abbreviations: CAMP = Childhood Asthma Management Program; GACRS = Genetics of Asthma in Costa Rica Study; BMI = body mass index; ICS = inhaled corticosteroids; Coef. = coefficient.