Exhaled breath condensate metabolomics reveals conserved networks and bidirectional crosstalk in asthma and CRSwNP

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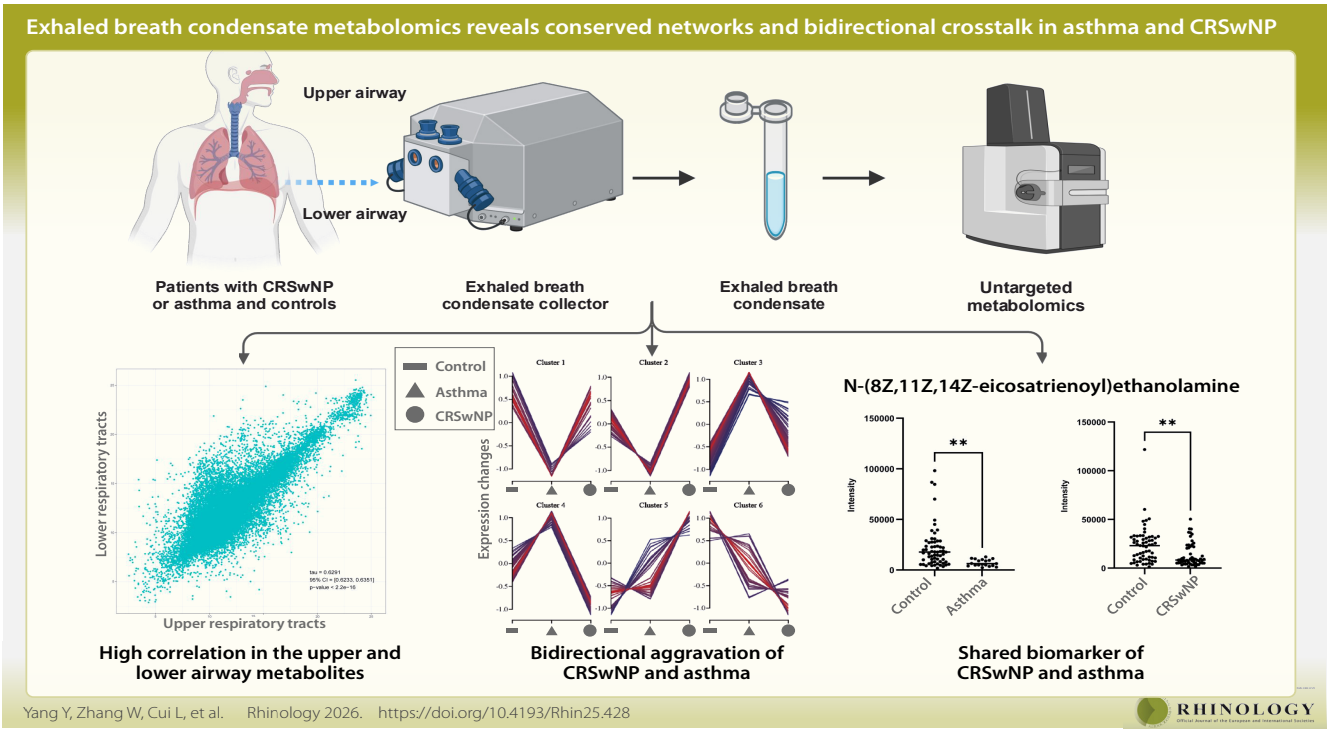

Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma frequently coexist. However, the metabolic interplay between those diseases is poorly understood. We aimed to perform metabolomic profiling of exhaled breath condensate (EBC) from CRSwNP and asthma patients and investigate possible interaction pathways. **Methodology**: EBC samples from the upper and lower airways of patients with CRSwNP, asthma, and control subjects were analyzed using untargeted metabolomics. Metabolite consistency and conserved modules between the upper and lower airways were quantified. WGCNA, trend clustering analysis, and a pathway enrichment analysis of differential metabolite expression were performed. **Results**: A total of 252 metabolites were identified, with a strong correlation between the upper and lower airway profiles. WGCNA analysis showed that each module of the upper or lower airway was conserved, with at least 1 module included in the consensus network. The key enriched pathways for lower airway metabolites showed a continuous increasing or decreasing trend in the control, CRSwNP, and asthma groups, and mainly involved the impact of CRSwNP on asthma. The main enriched pathways for upper airway differential metabolites in the control, asthma, and CRSwNP groups were related to the impact of asthma on nasal polyps. N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine was significantly down-regulated in the EBC of CRSwNP and asthma patients, and was negatively correlated with the risk for CRSwNP and asthma onset. Leukotriene F4 (LTF4) was up-regulated in the EBC of CRSwNP and asthma patients, and was positively correlated with the risk for CRSwNP onset. **Conclusion**: Non-invasive EBC metabolomics revealed conserved metabolic networks and bidirectional perturbations between CRSwNP and asthma, providing new evidence for the "unified airway" hypothesis.

Key words: chronic rhinosinusitis with nasal polyps, asthma, unified airway disease, exhaled breath condensate, metabolomics

Introduction

The concept of "one airway, one disease" emphasizes the connection between asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) [1]. The comorbidity of CRSwNP and asthma causes a huge economic burden [2], and both disorders share common anatomical, immunological, and pathophysiological bases [3,4]. Clinically, 7–15% of mild and 50–70% of severe asthma patients have CRSwNP, while 40–70% of CRSwNP patients have asthma, leading to worse symptoms and quality of life [5,6]. In clinical practice, the nose and lungs are often treated as separate entities, the treatment strategies for those coexisting entities are frequently insufficient [7]. Furthermore, comorbidities of CRSwNP and asthma are difficult to treat because very little is known about the underlying systemic inflammatory link between them. Exhaled breath condensate (EBC) contains molecular information that could provide insights into an individual's health, and it is obtained by cooling exhaled air and collecting the condensate [8,9]. EBC is a promising diagnostic tool because it can be collected rapidly, repeatedly, in a non-invasive manner, which is advantageous for both patients and clinical studies [10]. EBC metabolomic studies have been widely used to identify and diagnose airway diseases [11,12]. In this study, we performed a metabolomics analysis on EBC collected from the upper and lower airways of patients with CRSwNP or asthma to further provide proof for a unified airway.

Materials and methods

Participants

A total of 56 CRSwNP patients, 19 asthma patients, and 61 controls who visited Yantai Yuhuangding Hospital from June 2021 to March 2022 were enrolled in the study (Table 1). CRSwNP was diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [13]. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) [14]. Patients with concomitant inflammatory diseases such as autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease) or with other sinonasal and nasal tumors were excluded. Additionally, patients with acute respiratory infections within the 4 weeks prior to sample collection, those using systemic corticosteroids or immunomodulators for non-asthma/non-CRSwNP conditions, and those diagnosed with COPD, bronchiectasis, or other chronic lung diseases were also excluded. No patients in the CRSwNP group had asthma, and no patients in the asthma group had CRSwNP. Each patient provided their signed informed consent for study participation. The study protocol was approved by the Human Ethics Committee of Yantai Yuhuangding Hospital (Approval number: 2020-287). Nasal polyp size was graded according to the EPOS guidelines (13) as: 0 = no polyps; 1 = polyps confined to the middle meatus; 2 = polyps beyond the middle meatus.

Clinical sample acquisition

EBC samples were collected between 8 and 10 AM after a 6–8 hour fast. Condensation temperature was set to −100°C, with collection beginning 5 minutes after the patient achieved calm breathing. As no upper-airway-specific EBC collection device currently exists, we developed a novel condenser to separately collect EBC from the upper and lower respiratory tracts. The device was operated by having the patient blow air through an inert mouthpiece. An olive-tipped tube was inserted into one nostril to create a seal. Upon blowing, the soft palate elevated, temporarily separating the oropharynx from the nasopharynx and preventing mixing with lower airway air. Concurrently, a negative-pressure system activated automatically, drawing air at a fixed flow rate of 10 mL/s from the contralateral nostril. This air passed through the posterior nasal cavity and both nasal passages, carrying nasal metabolites. This principle is identical to that employed in the standardized clinical measurement of nasal nitric oxide (nNO). Lower airway EBC was collected as previously described [15]. Condensation droplets, totaling approximately 100–200 µL were added to a pre-cooled methanol/acetonitrile/water mixture (2:2:1, v/v) and vortexed. After a low-temperature ultrasonic water bath for 30 min, the samples were allowed to stand at -20°C for 10 min, centrifuged at 14,000g at 4°C for 20 min, after which, the supernatants were removed and dried under vacuum. The samples to be analyzed were dissolved in 100 µL of acetonitrile-water solution (acetonitrile: water = 1:1, v/v), vortexed, and centrifuged at 14,000g at 4°C for 15 min; after which, each supernatant was fed into a chromatography-mass spectrometer (chromatography-MS) for analysis. Aliquots of the supernatant for all samples were mixed to prepare quality control (QC) samples.

Untargeted metabolomics analysis

Samples were separated on an Agilent 1290 Infinity LC ultra-high performance liquid chromatography system (UHPLC) and analyzed on a Triple TOF 6600 mass spectrometer (AB SCIEX) using electrospray ionization (ESI) positive ion, and negative ion modes, respectively.

The original data were converted into mzXML format by ProteoWizard, and then peak alignment, time correction, and peak area extraction were performed by XCMS software. The data extracted by XCMS were subjected to metabolite structure identification and data pre-processing, followed by experimental data quality evaluation, and finally, data analysis. Metabolite identification was performed by matching the accurate mass (mass error < 10 ppm) and MS/MS spectra against the Human Metabolome Database (HMDB) and our in-house spectral library.

Data analysis

After sum-normalization, multivariate data analyses, including Pareto-scaled principal component analysis (PCA) and weighted

Table 1. Baseline characteristics of the study participants.

	Control (n = 61)	CRSwNP (n = 56)	Asthma (n = 19)	P-value
Demographics				
Sex (male, %)	21 (34.43%)	21 (37.5%)	6 (31.58%)	0.88
Age (years)	45.41 ± 8.80	46.29 ± 9.39	40.74 ± 11.74	0.09
Smoking (n, %)	16 (26.23%)	16 (28.57%)	3 (15.79%)	0.59
BMI (kg/m^2)	24.97 ± 2.84	26.28 ± 3.23	26.83 ± 4.81	0.10
Combined allergic rhinitis (n, %)	0	5 (8.93%) [a]	7 (36.84%) [a,b]	< 0.001
Inflammatory Marker				
Blood eosinophil absolute count (×10^9)	0.16 ± 0.15	0.28 ± 0.21 [a]	0.38 ± 0.34 [a]	< 0.001
CRSwNP-specific characteristics				
Lund-Mackay CT scores		12.77 ± 5.90		
Nasal polyp size		3.30 ± 1.56		
Prior surgery history (n, %)		23 (41.07%)		
Eosinophilic CRSwNP (n, %)		30 (53.57%)		
Asthma-specific Characteristics				
Asthma Control Test (ACT) score			18.32 ± 3.58	
Exacerbations in past year (n)			2.95 ± 2.86	
Medication Use, n (%)				
ICS+LABA			19 (100%)	
Eosinophilic asthma (n, %)			14 (73.68%)	

[a]: P < 0.05 when compared with the control group; [b]: P < 0.05 when compared with the CRSwNP group. No patients in the CRSwNP or Asthma groups had a physician-confirmed diagnosis of the other disease.

gene co-expression network analysis (WGCNA), were performed using the R package (ropls). FC > 1.5 or FC < 0.67 in conjunction with a P value < 0.05 were used to screen for significantly changed metabolites. Allergic rhinitis (AR) status was included as a binary covariate in all univariate statistical models. The R package 'Mfuzz' (2.66.0) was used to cluster molecules with similar changing trends among control subjects, CRSwNP patients, and asthma patients.

CRSwNP patients were classified based on the count of eosinophils per high-power field (≥55/HPF defined as eosinophilic type) in nasal polyp histopathological sections; asthma patients were stratified according to peripheral blood eosinophil count (>0.15×10^9/L defined as eosinophilic asthma). Subsequently, partial least squares-discriminant analysis (PLS-DA) was performed for each endotype. The results demonstrated substantial overlap between eosinophilic and non-eosinophilic endotypes in both diseases, with poor model predictive performance (Q^2 = -0.0608 and -0.188 for CRSwNP and asthma, respectively). This indicated that the eosinophilic endotype did not confer a distinct metabolic signature in our EBC dataset.

Statistical analysis

Statistical analyses were performed using GraphPad Prism. Participant characteristics are presented as mean ± SD for continuous variables and as N (%) for categorical variables. Group comparisons were conducted using two-tailed Student's t-tests (continuous) or χ^2 tests (categorical), with ANOVA applied for multi-group analyses. A two-sided P value < 0.05 was considered statistically significant.

Results

Quality control assessment

The percentage of metabolites detected across QCs is 100% (Table S1). The QC samples were closely clustered together, suggesting good repeatability of the experiment (Figure S1A). A Pearson correlation analysis was conducted on the QC samples (Figure S1B). The correlation coefficients between the QC samples are all above 0.9, indicating good experimental repeatability. The multivariate control chart for the QC samples of this project is shown in Figure S1C. The QC samples are all within the range of ±3 standard deviations, indicating that the instrument's fluctuations are within the normal range. The results of Hotelling's T2 test are shown in Figure S1D. The QC samples are all within the 99% confidence interval, which means that the repeatability of the experiment is good.

Metabolite expression profiles in the EBC samples from the upper and lower airway

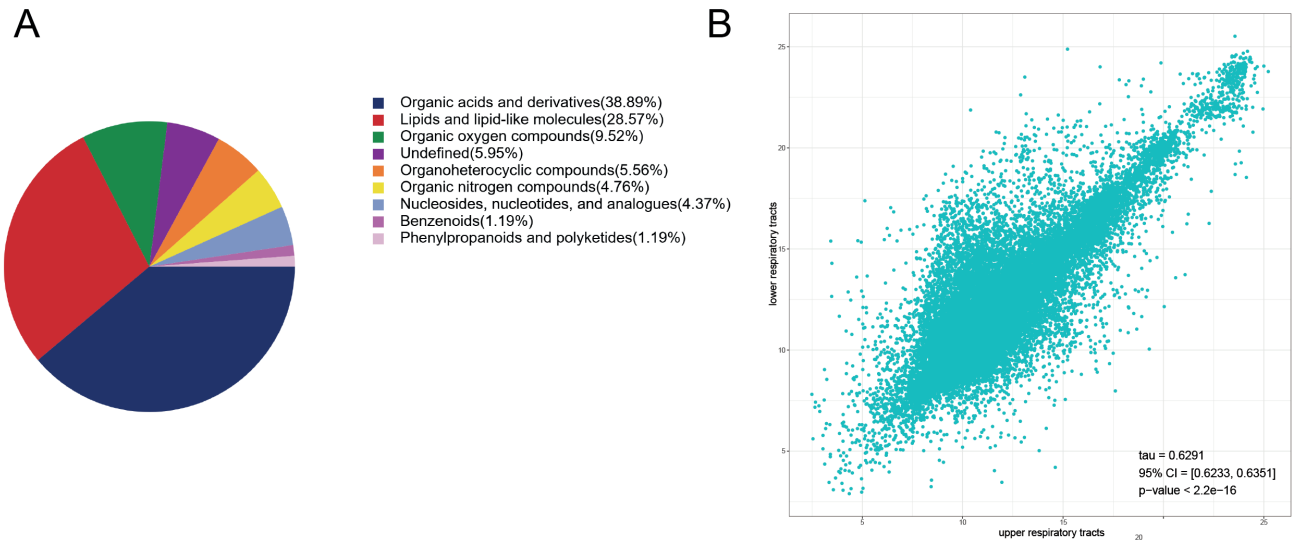

Figure 1. Metabolite expression profiles in exhaled breath condensate (EBC) from the upper and lower airways. (A) Pie chart showing the classification of identified metabolites in samples of EBC from patients with chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and control subjects. (B) Scatter plot with a Kendall's tau correlation analysis of the upper and lower airway metabolite profiles. Each point represents a single metabolite.

A total of 252 metabolites were identified in all the samples. The metabolites were classified into ten categories, including Organic acids and derivatives (38.89%); Lipids and lipid-like molecules (28.57%); Organic oxygen compounds (9.52%); Undefined (5.95%); Organoheterocyclic compounds (5.56%); Organic nitrogen compounds (4.76%); Nucleosides, nucleotides, and analogues (4.37%); Benzenoids (1.19%); Phenylpropanoids and polyketides (1.19%) (Figure 1A). Kendall's tau correlation coefficient showed a high correlation between metabolites in the upper and lower airways ($\tau = 0.63$, 95% CI: 0.62–0.64, $P < 0.01$) (Figure 1B).

Assessment of upper and lower airway unity by WGCNA

We performed a WGCNA analysis to identify modules with similar annotation patterns and identified 4 modules with similar metabolite annotation patterns in the upper or lower airway samples, respectively (Figures 2A and 2B). Each module of the upper airway was conserved by at least 1 module in the lower airway; similarly, each module of the lower airway was conserved by at least 1 module of the upper airway (Figure 2C). A KEGG pathways enrichment analysis of each module is shown in Figures S2 and S3.

Next, we constructed a consensus network with 4 modules based on all the metabolites in the upper and lower airways (Figure 2D). The metabolic architecture of the unified airway was analyzed by mapping regional airway modules onto fundamental consensus modules. This "many-to-many" mapping, illustrated in Figures 2E and 2F, shows that core consensus modules serve as reusable functional units. Individual regional modules frequently drew from multiple consensus modules, and each consensus module contributed to several regional networks. The median fold-change in metabolite annotation of each consensus module was <2 across all phenotypes (Figure 2G), indicating limited variation between upper and lower airway networks regardless of disease or control status. Metabolites in the grey module showed no significant differential expression between airway regions and were enriched in the "Arginine and proline metabolism" pathway (Figure 2H).

Key metabolites and pathways involved in the effect of CRSwNP on asthma

To elucidate the molecular mechanism underlying the impact of CRSwNP on asthma, all metabolites of the lower airway in the control, CRSwNP, and asthma groups were analyzed and were clustered into 6 clusters (Figure 3A). The metabolites in cluster 4 showed a stepwise decrease from the control group to the CRSwNP group and were lowest in the asthma group. They were enriched in "Pyruvate metabolism", "Propanoate metabolism", "Tyrosine metabolism", "Citrate cycle (TCA cycle)", "Glucagon signaling pathway" and so on (Figure 3B). Conversely, the metabolites in cluster 6 showed a stepwise increase from the control group to the CRSwNP group and were highest in the asthma group, and they were enriched in "Biosynthesis of unsaturated fatty acids", "Biotin metabolism", "ABC transporters", "Fatty acid biosynthesis", "Epithelial cell signaling in Helicobacter pylori infection" and so on (Figure 3C). The KEGG pathway enrichment analysis on metabolites from all clusters are available in the Table S2.

Key metabolites and pathways involved in the effect of asthma on CRSwNP

Similarly, all metabolites from the upper airway were clustered

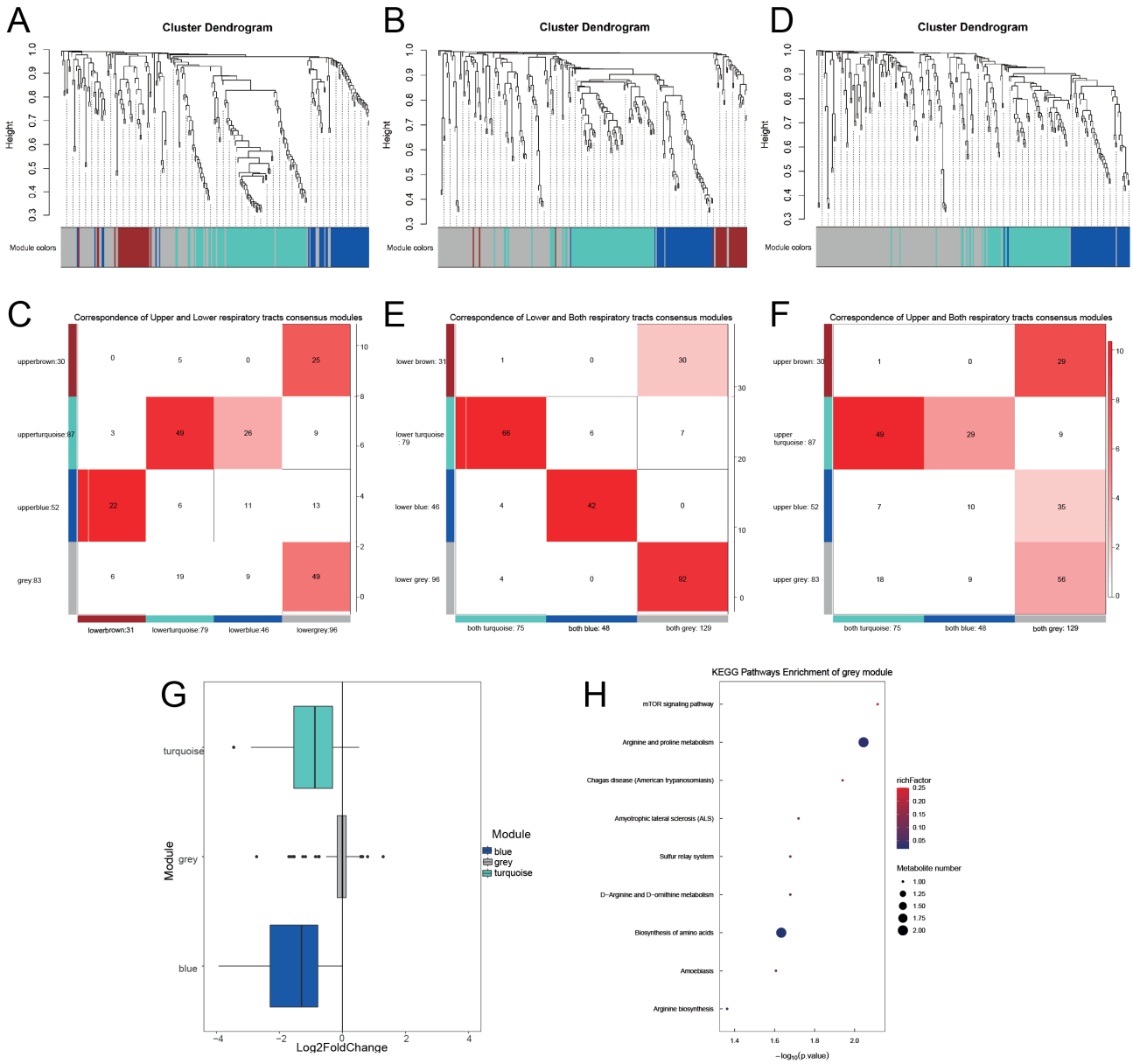

Figure 2. Weighted gene co-expression network analysis (WGCNA) analysis of conserved metabolic modules in the upper and lower airways. (A-B) Dendrograms and module assignments (color-coded) for metabolites in the (A) upper and (B) lower airway networks. (C) Overlap heatmap showing significant conservation of metabolic modules between the upper and lower airways. Each cell represents the degree of overlap (conservation) between modules from the two regions. (D) Dendrogram module assignment (color-coded) for upper and lower airway metabolites. (E-F) Overlap heatmap between consensus modules and (E) upper or (F) lower airway modules. (G) Box plots of median fold-change differences in module annotations between the upper and lower airways. (H) KEGG pathway enrichment of grey module in the consensus network.

into 6 clusters based on their expression trends in the control, asthma, and CRSwNP groups (Figure 4A). The metabolites in cluster 5 showed a stepwise increase from the control group to the asthma group and were lowest in the CRSwNP group. They were involved in "Sphingolipid signaling pathway", "cAMP signaling pathway", "Choline metabolism in cancer", "Glycerophospholipid metabolism", "Nucleotide metabolism", "Sphingolipid metabolism", and so on (Figure 4B). In contrast, the metabolites in cluster 6 were enriched in "Mineral absorption", "Pantothenate and CoA biosynthesis", "beta-Alanine metabolism", "Phenylalanine, tyrosine and tryptophan biosynthesis", "Central carbon metabolism in cancer", and so on (Figure 4C). The KEGG pathway enrichment analysis on metabolites from all clusters are available in the Table S3.

N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and leuko-

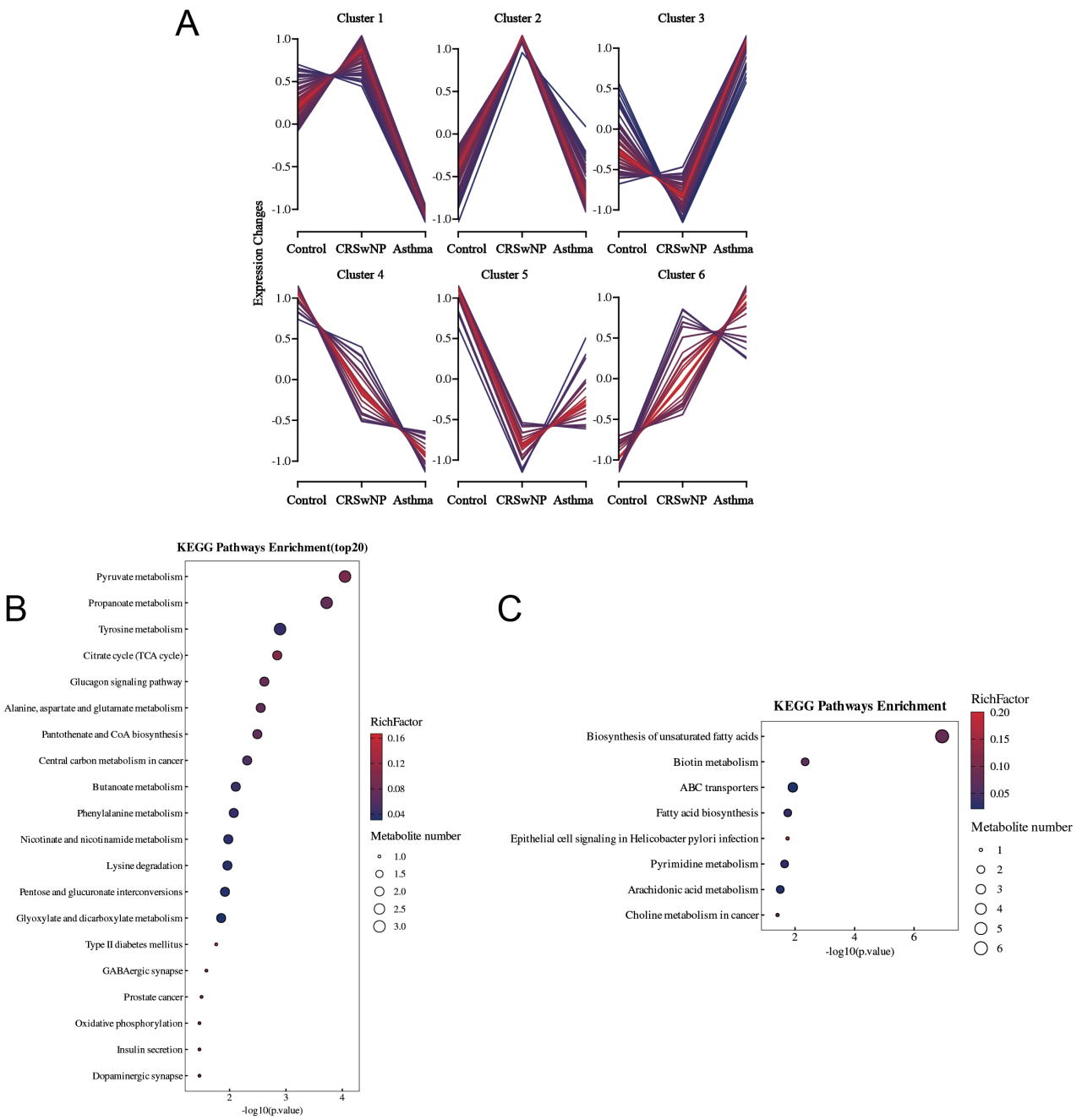

Figure 3. Key metabolites and pathways in the lower airway across the control, CRSwNP, and asthma spectrum. (A) MFuzz clustering of metabolites in the lower airway across the control, CRSwNP, and asthma groups. Metabolite abundance values were Z-score standardized prior to fuzzy c-means clustering. (B) KEGG enrichment of metabolites in Cluster 4. (C) KEGG enrichment of metabolites in Cluster 6.

triene F4 (LTF4) were identified as key shared metabolites in both CRSwNP and asthma patients

Eight up-annotated metabolites and 16 down-annotated metabolites were detected in the upper airway of CRSwNP patients when compared with the control group (Figure 5 A). They were enriched in "Sphingolipid signaling pathway", "Sphingolipid metabolism" and "Arginine and proline metabolism" (Figure 5B). Thirty-five up-annotated metabolites and 12 down-annotated metabolites were detected in in the lower airway of asthma patients when compared with the control group (Figure 5C). They were enriched in pathways such as "Biosynthesis of unsaturated fatty acids", "Central carbon metabolism in cancer", "Fatty acid biosynthesis", "mTOR signaling pathway", "Chagas disease", and so on (Figure 5D). N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and LTF4 were the key metabolites that were either down-annotated or up-annotated in the EBC of both the upper airway of CRSwNP patients and the lower airway of asthma patients (both P-values < 0.05) (Figure 5E and F). A logistic regression analysis

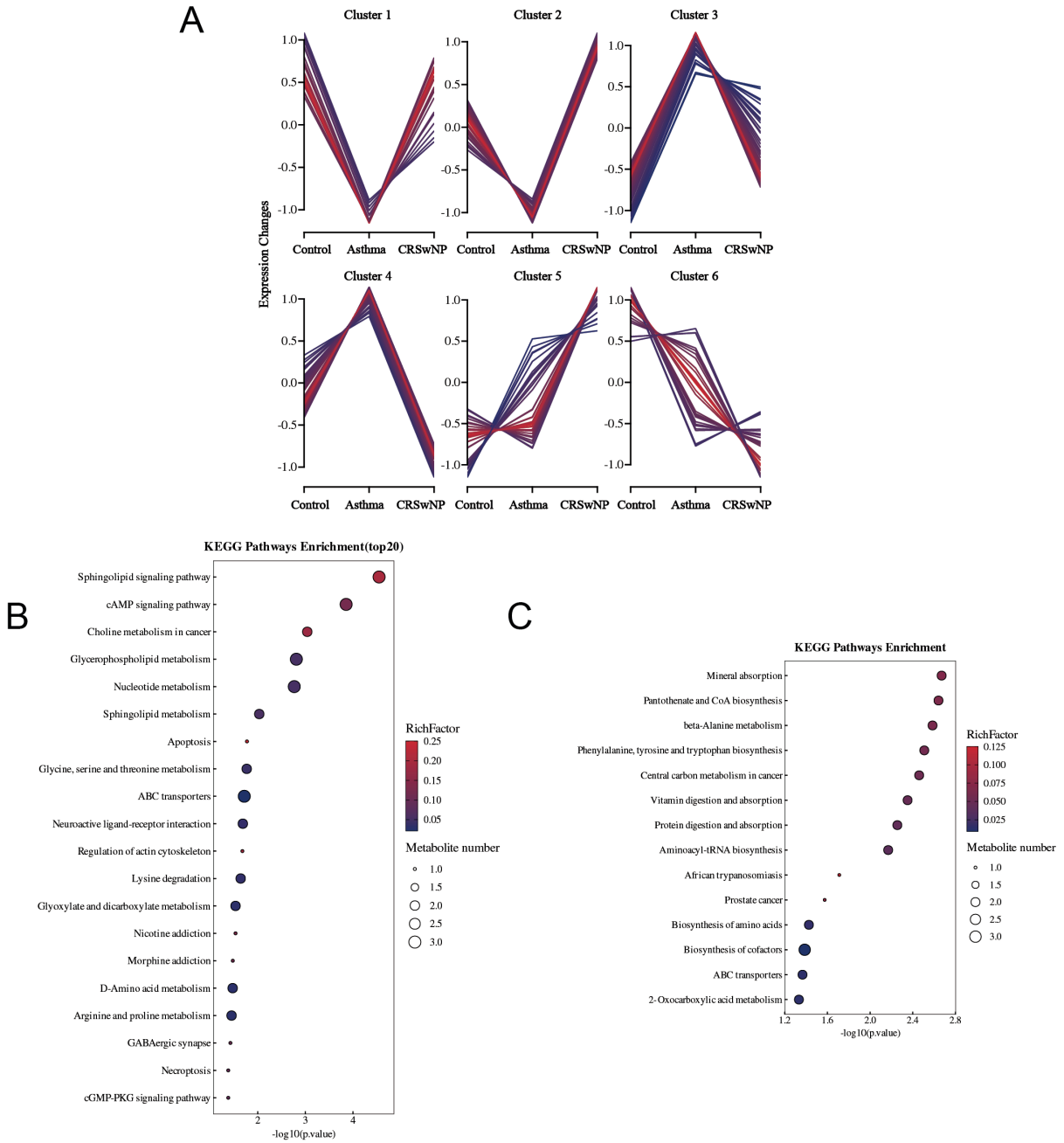

Figure 4. Key metabolites and pathways in the upper airway across the control, asthma, and CRSwNP spectrum. (A) MFuzz clustering of metabolites in the upper airway across the control, asthma and CRSwNP groups. Metabolite abundance values were Z-score standardized prior to fuzzy c-means clustering. (B) KEGG enrichment of metabolites in Cluster 5. (C) KEGG enrichment of metabolites in Cluster 6.

revealed that lower levels of metabolite N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine was negatively correlated with the risk for CRSwNP, with an odds ratio (OR) of 0.57 (95% CI: 0.41–0.78, P < 0.01). At the same time, N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine was negatively correlated with the risk for asthma, with an OR of 0.33 (95% CI: 0.16–0.57, P < 0.01) (Figure 5G). The upper level of LTF4 was positively correlated with the risk for CRSwNP, with an OR of 1.75 (95% CI: 1.28–2.47, P < 0.01). LTF4 showed no significant association with asthma risk (OR = 0.94, 95% CI: 0.69–1.24, P = 0.68) (Figure 5H).

We performed Spearman correlation analyses between N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine, LTF4 and available clinical indices (Table S4). In the lower airway of asthma, N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine exhibited a positive correlation with FeNO (r = 0.598, P = 0.024). Furthermore, LTF4 showed a positive correlation with the FEV_1/FVC ratio (r = 0.463, P = 0.046). In contrast, within the upper airway of CRSwNP patients, neither N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine nor

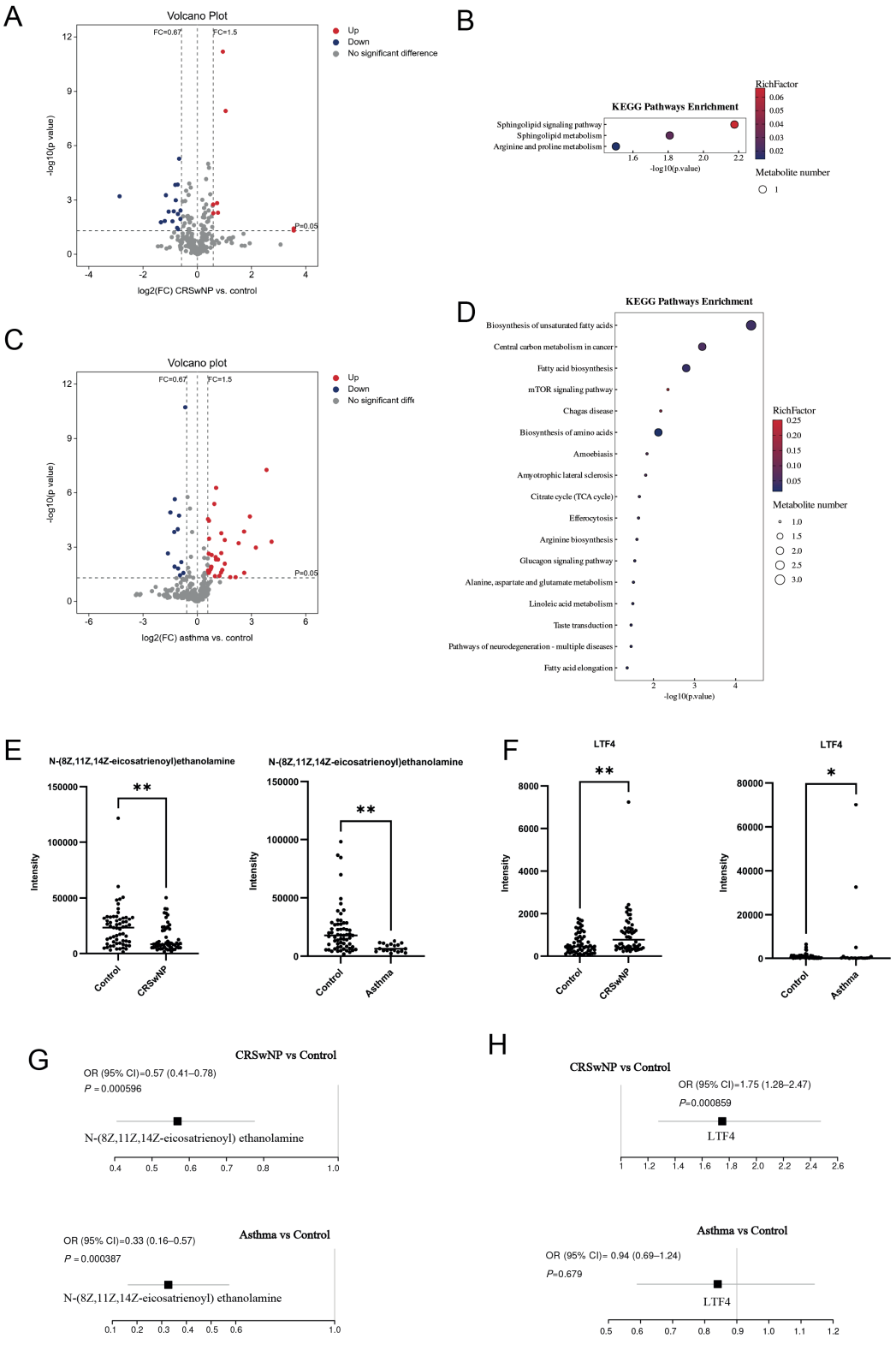

Figure 5. Identification of N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and leukotriene F4 (LTF4) as shared metabolites in CRSwNP and asthma. (A) Volcano plots of differentially annotated metabolites in CRSwNP vs. control. (B) KEGG pathway enrichment of differentially annotated metabolites in CRSwNP vs. control. (C) Volcano plots of differentially annotated metabolites in asthma vs. control. (D) KEGG pathway enrichment of differentially annotated metabolites in asthma vs. control. (E-F) Box plots comparing the relative abundance of N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine (E) and LTF4 (F) in the upper airway of CRSwNP patients and the lower airway of asthma patients versus their respective control groups. *P < 0.05, **P < 0.01. (G) Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lower levels of N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and the risk of CRSwNP and asthma. (H) ORs and 95% CIs for the association between higher levels of LTF4 and the risk of CRSwNP and asthma.

LTF4 showed any significant correlation with clinical parameters, including nasal endoscopy score, Lund-Mackay CT score, blood eosinophil counts, or lung function indices (all $P > 0.05$). Compared to the asthma group, CRSwNP patients showed 26 upregulated and 60 downregulated metabolites in the upper airway (Figure S4A). These metabolites were enriched in local lipid metabolism and signaling pathways, including "Fatty acid biosynthesis" and "Sphingolipid signaling/metabolism" (Figure S4B). In the lower airway, CRSwNP had 19 upregulated and 40 downregulated metabolites (Figure S4C), linked to systemic metabolic reprogramming and neuro-immune interactions, with enrichments in pathways such as "mTOR signaling" and "Aminoacyl-tRNA biosynthesis" (Figure S4D). Notably, both airway levels shared enrichments in core pathways including the "Citrate cycle (TCA cycle)" and "Alanine/aspartate/glutamate metabolism".

Discussion

The "unified airway" hypothesis considers the respiratory tract a continuous entity, supported by targeted therapies that improve both asthma and upper airway outcomes [16-19]. Our study provides novel metabolomic evidence by analyzing EBC samples from upper and lower airways. We found that metabolic networks were conserved and correlated across both sites, indicating functional metabolic unity. Additionally, we identified bidirectional metabolic pathways through which CRSwNP and asthma may exacerbate each other: CRSwNP influences asthma via enhanced lipid inflammatory pathways (e.g., arachidonic acid metabolism), while asthma affects CRSwNP through pathways related to cellular signaling and stress (e.g., sphingolipids). A shared systemic biomarker signature—downregulation of the anti-inflammatory mediator N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and upregulation of pro-inflammatory LTF4—further indicates a systemic inflammatory imbalance.

In recent years, multi-omic technologies have provided new perspectives for revealing the common pathogenesis of upper and lower airway diseases [20,21]. In our study, the high correlation (Kendall's tau = 0.63, $P < 0.01$) between upper and lower airway metabolites supported the systemic nature of airway inflammation in CRSwNP and asthma. WGCNA revealed conserved metabolic modules across both regions, with each module in the upper airway significantly overlapping with at least one module in the lower airway. The consensus network analysis further validated this unity, demonstrating that metabolic modules in both regions significantly overlapped with consensus pathways. This modular conservation, coupled with minimal fold-change differences (< 2-fold) in pathway annotations underscores shared metabolic perturbations in both diseases. These findings reinforce the concept that CRSwNP and asthma are not isolated entities [22,23]. The metabolites in the grey module of the consensus network were enriched in the "Arginine and proline metabolism", a pathway linked to Th2 inflammation via nitric oxide overproduction [24,25]. This aligns with the clinical efficacy of type 2-targeting biologics (e.g., anti-IL-4/IL-13) in improving both upper and lower airway symptoms [26], supporting their potential to correct systemic metabolic dysregulation in comorbid patients.

To elucidate how CRSwNP influences asthma pathogenesis, we identified distinct metabolic clusters associated with disease progression. Metabolites in cluster 6, which showed an increasing trend, were enriched in pathways such as "Biosynthesis of unsaturated fatty acids" and Arachidonic acid metabolism". These pathways are central to the production of lipid mediators that drive type 2 inflammation and airway remodeling, as seen with elevated arachidonic acid derivatives (e.g., PGE2, LTB4) in CRSwNP that promote eosinophil recruitment and bronchial hyperreactivity in asthma [27-29]. This suggests that CRSwNP-associated lipid dysregulation could amplify lower airway inflammation and contribute to asthma severity. Conversely, cluster 4 metabolites were linked to "Pyruvate metabolism" and the "TCA cycle." Their downregulation in CRSwNP may reflect systemic oxidative stress, which is known to impair airway epithelial repair and exacerbate asthma symptoms [30]. This metabolic shift may reduce ATP availability, impair mucociliary clearance, and increase susceptibility to bronchoconstriction, providing a mechanistic link between CRSwNP and asthma severity.

In examining how asthma affects CRSwNP, the metabolites in cluster 5 showed an increasing trend and were involved in pathways including the "Sphingolipid signaling pathway" and "cAMP signaling pathway". Sphingolipids can regulate the functions of immune cells and the production of cytokines, thereby influencing the severity and progression of various diseases [31,32]. Dysregulation of the "cAMP signaling pathway" affects the contractility of airway smooth muscle and the release of inflammatory mediators, which is related to the asthma pathogenesis [33,34]. Conversely, the metabolites in cluster 6 showed a downward trend and were enriched in pathways such as the "Mineral absorption", "Protein digestion and absorption", and "Aminoacyl-tRNA biosynthesis". This pattern may reflect a concurrent dysregulation of nutrient metabolism and anabolic processes, potentially indicating a heightened demand for biosynthesis or an impairment of metabolic homeostasis that could influence tissue repair and immune function [35-37].

In this study, N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine was downregulated in both CRSWNP and asthma, suggesting its potential to serve as a unified biomarker. Lower levels of this metabolite were closely associated with an increased risk for those diseases, indicating its value for early diagnosis and risk stratification. Structurally, it resembles known N-Acyl Ethanolamines (NAEs), which exert anti-inflammatory and immunomodulatory effects via multiple receptors [38,39]. The positive correlation between N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine and FeNO

in asthma points to a link with type 2 inflammation [40], while the absence of correlation in CRSwNP may reflect the integrated local-systemic nature of upper-airway EBC. We also identified LTF4 as a consistently upregulated pro-inflammatory mediator in both diseases. LTF4 is a canonical cysteinyl leukotriene, a potent pro-inflammatory mediator derived from arachidonic acid metabolism that drives eosinophilic inflammation and airway remodeling—core features of both diseases. Its systemic elevation across the unified airway provides molecular evidence for a shared inflammatory mediator milieu. Although a preliminary correlation was observed between LTF4 and lung function in asthma, larger cohorts are needed to rule out confounding. Together, the upregulation of LTF4 and downregulation of N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine suggest a pathogenic imbalance between pro-inflammatory and pro-resolving signals, which may perpetuate inflammation across both airway compartments and explain their frequent co-aggravation.

Our findings reveal conserved metabolic networks, supporting the concept of systemic inflammatory coupling in the unified airway. This systemic view is consistent with well described tissue specific variations—such as in local microbiome or remodeling patterns—which add phenotypic nuance but do not contradict the overarching hypothesis [41,42]. For instance, Kanemitsu et al. [43] showed that a systemic biomarker (sputum periostin) specifically correlated with upper airway inflammation and olfactory function, illustrating how a shared systemic driver can produce region specific manifestations. Thus, we propose a refined model in which a common systemic inflammatory drive interacts dynamically with local factors, generating distinct yet interconnected phenotypes.

A key question concerns the origin of the observed metabolic signals. Our EBC device employs the same physiological principle of nNO measurement to enrich local constituents. Therefore, like nNO as a local readout of systemic immune status, our EBC metabolomic profile may represent localized manifestations of a systemic metabolic dysfunction. The conserved metabolic disturbances we observed across both airways nevertheless suggest that these signals likely derive from, or are strongly modulated by, a shared systemic inflammatory milieu, consistent with the efficacy of systemic biologics in unified airway disease [44].

This study has some limitations. First, although the sample size was sufficient for an exploratory analysis, it needs to be expanded to confirm the findings. Second, clarifying the contributions of systemic versus local pathways requires correlating EBC profiles with direct tissue analyses in future studies. Third, the functional role of N-(8Z,11Z,14Z-eicosatrienoyl) ethanolamine remains speculative and requires experimental validation. Fourth, focusing on 'pure' CRSwNP and asthma cases without comorbidity clarifies disease-specific signals but limits insight into potential synergistic metabolic effects in comorbid conditions. Future studies in comorbid populations are essential to validate these interactions. Fifth, the reproducibility of EBC collection is challenging, as reflected by variable CVs for key metabolites (Table S5), and future studies should adopt standardized devices and protocols. Finally, while significant correlations were found between metabolites and clinical parameters in asthma, no such associations were observed in CRSwNP. This underscores the need for future studies to incorporate more comprehensive clinical datasets for CRSwNP.

Conclusion

In this study, EBC was obtained by condensing exhaled gas, thereby avoiding the trauma of bronchoalveolar lavage, sinus lavage or blood collection. In addition, by comparing the EBC of the upper airway and lower airway, the distribution patterns of metabolites in the unified airway were revealed. These findings underscore the importance of systemic therapeutic strategies and biomarker-driven approaches in management of co-existing airway diseases. Certainly, the "unified airway" does not imply that the disease phenotypes of the upper and lower airways are entirely identical. Local anatomical structures, microbiota, and tissue microenvironments confer distinct disease characteristics. This highlights that future research and treatment strategies need to further elucidate and target locally specific drivers while acknowledging the systemic commonalities.

Author contributions

Conceptualization: XS, YY, and YZ; Methodology: YY, WZ, and LC; Formal analysis: YY, WZ, LC, HY, YC, DW, JW; Investigation: YY, YZ and XS; Resources: YY, YZ and XS; Data Curation: YZ and XS; Writing: YY, WZ and LC; Visualization: YZ; Supervision: XS; Funding Acquisition: YZ and XS.

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Conflict of interest

The authors declare no competing interests.

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Data availability

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Xicheng Song (drxchsong@163.com).

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SUPPLEMENTARY MATERIAL

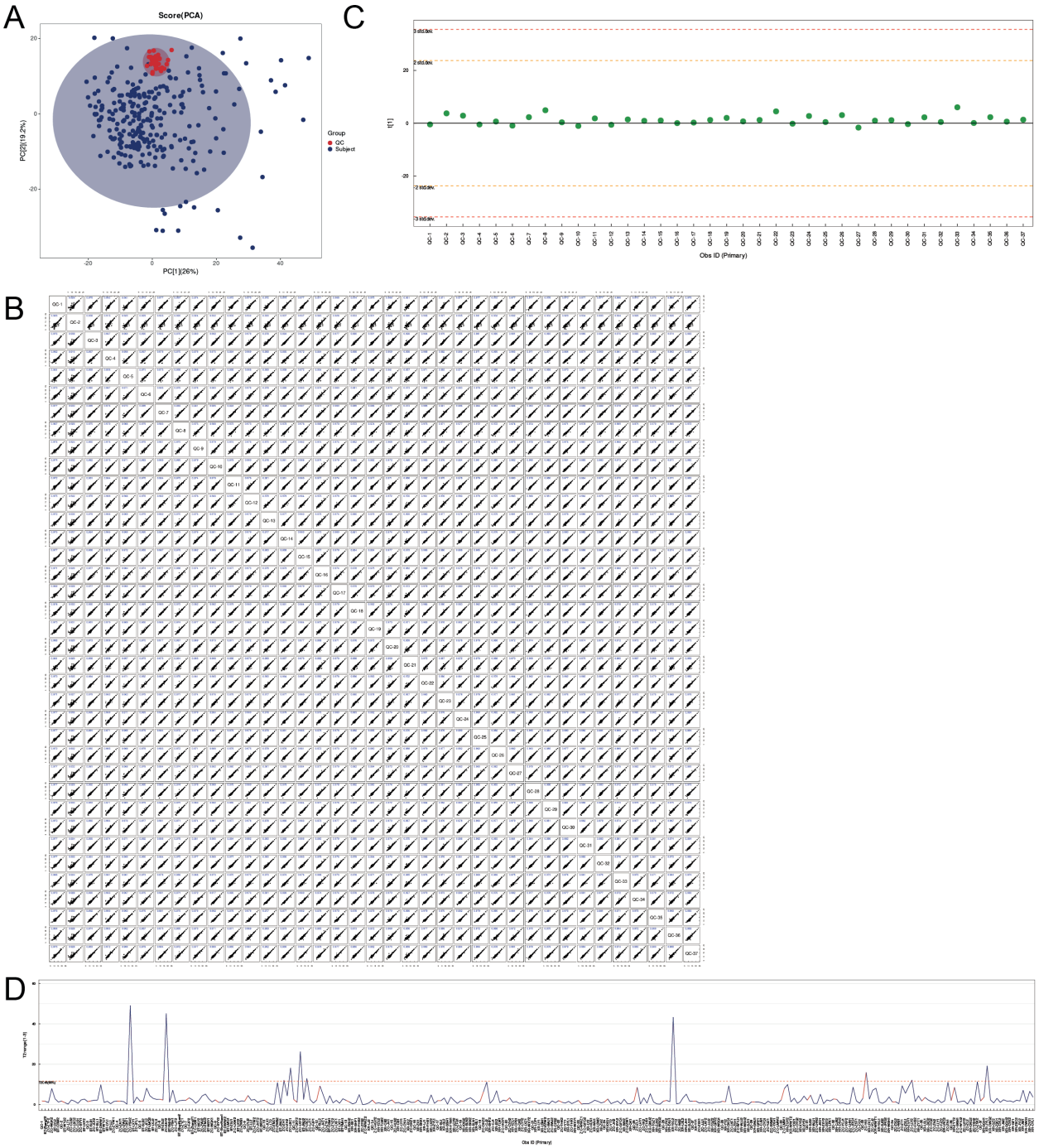

Figure S1. Quality control assessment. (A) Principal Component Analysis (PCA) scores plot of all experimental samples and quality control (QC) samples. (B) Pearson correlation matrix of QC samples. Correlation coefficients between all QC sample pairs are displayed. (C) Multivariate control chart (MCC) monitoring instrument stability. Each point represents a QC sample plotted against its injection order. (D) Hotelling's T2 plot for outlier detection. The plot displays the multivariate distance of each sample (experimental and QC) from the model center.

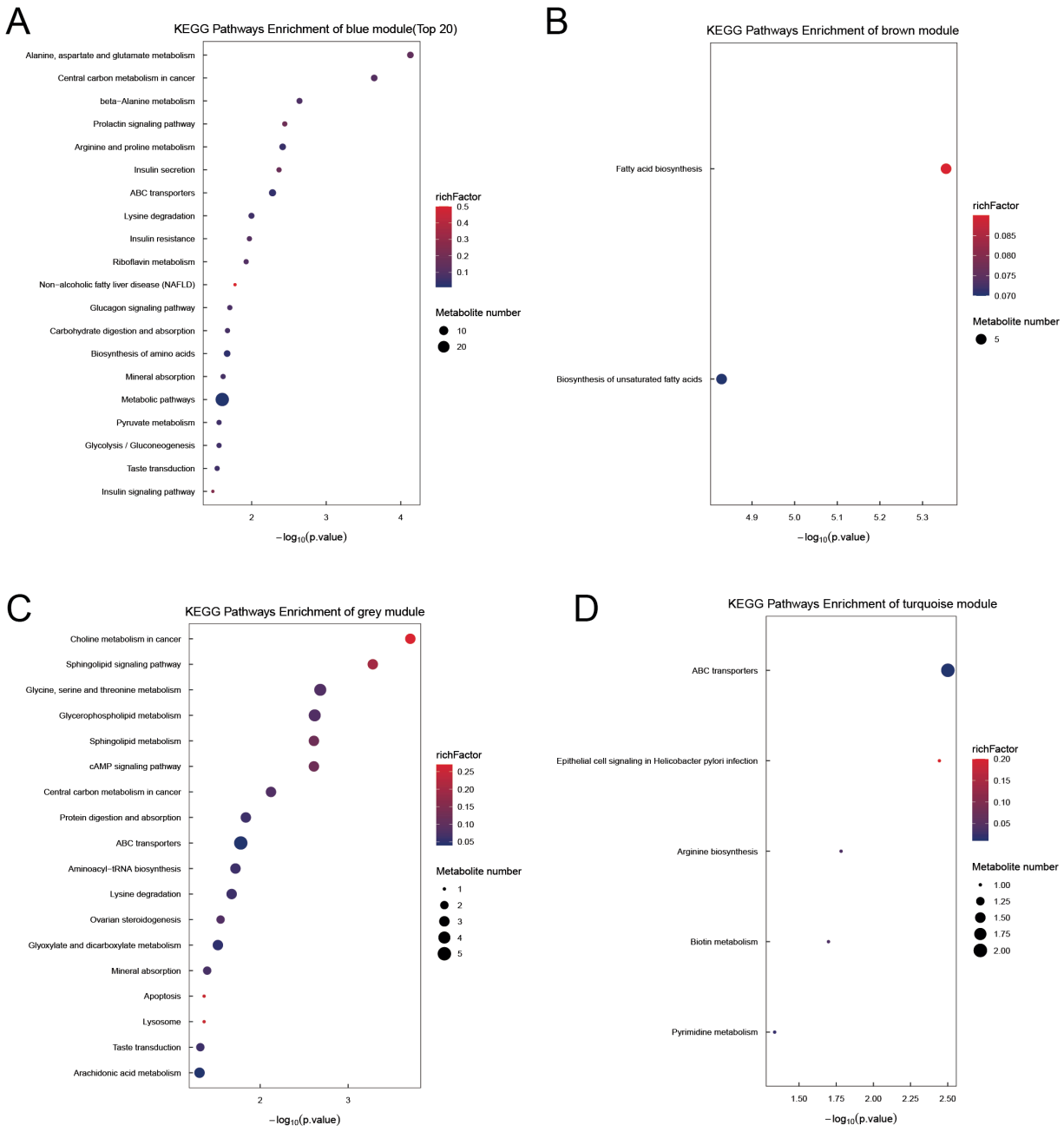

Figure S2. KEGG pathway enrichment of WGCNA modules in the upper airway.

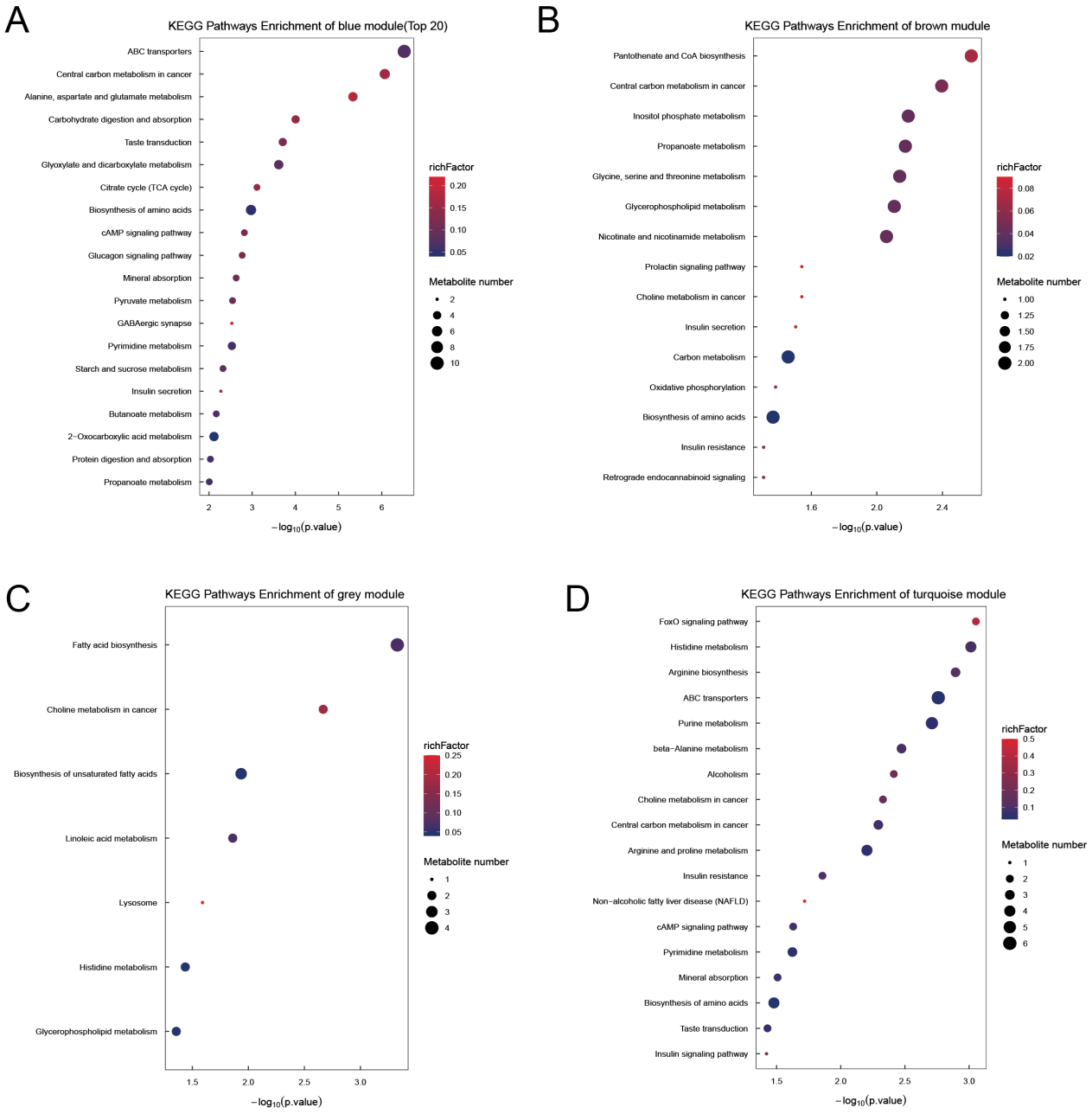

Figure S3. KEGG pathway enrichment of WGCNA modules in the lower airway.

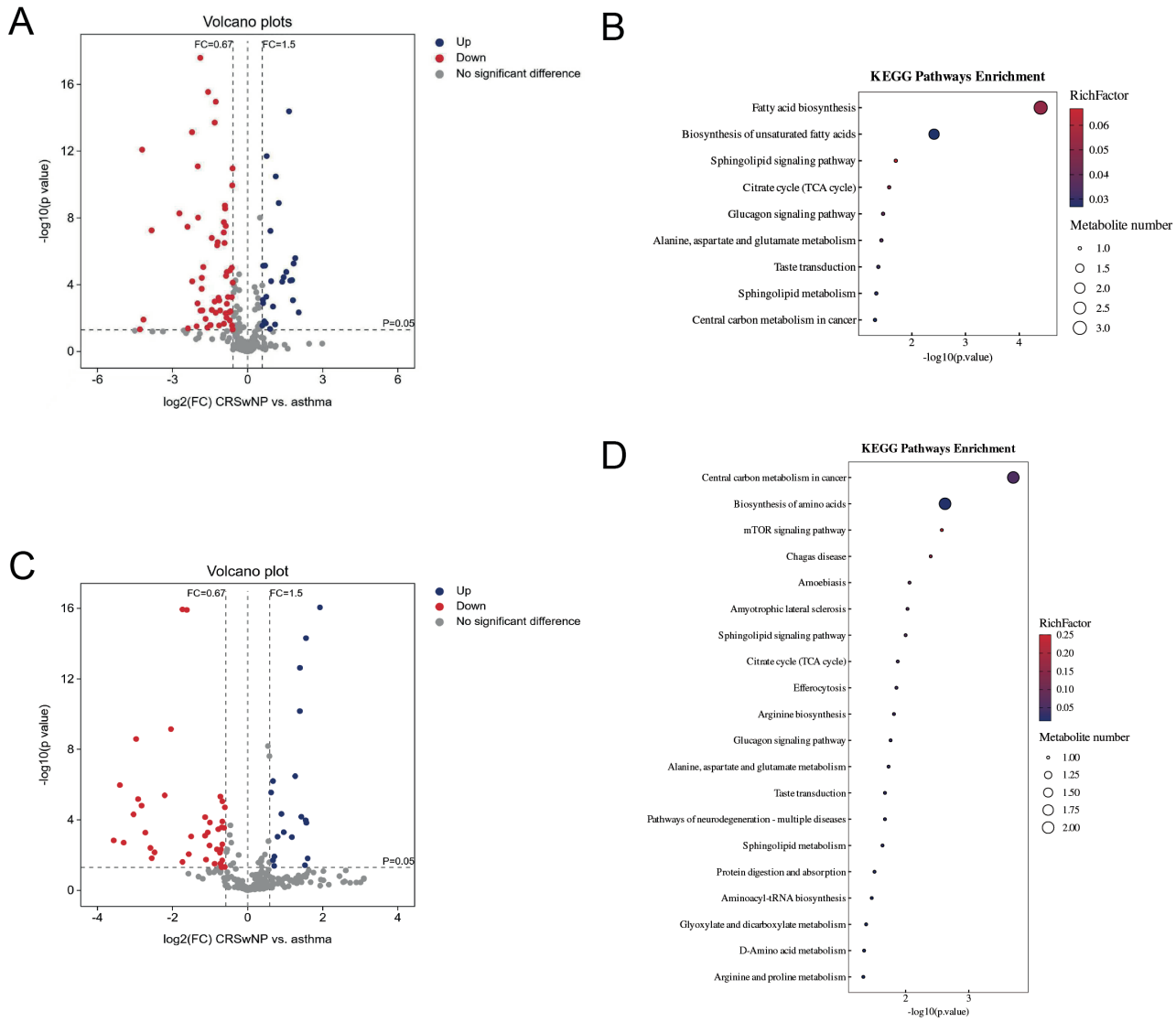

Figure S4. Key metabolites and pathways in the upper and lower airway between CRSwNP and asthma patients. (A) Volcano plots of differentially annotated metabolites of CRSwNP vs. asthma in the upper airway. (C) KEGG enrichment of differentially annotated metabolites of CRSwNP vs. asthma in the upper airway. (C) Volcano plots of differentially annotated metabolites of CRSwNP vs. asthma in the lower airway. (D) KEGG enrichment of differentially annotated metabolites of CRSwNP vs. asthma in the lower airway.

Table S1. Metabolites identified in all samples.

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M87T361	87.04	361.26	(R)-3-Hydroxybutyric acid	level 1	(M+H-H2O)+	0.96	HMDB0000011/ HMDB0000357	C01089	Organic acids and derivatives	Hydroxy acids and derivatives
M265T36	265.25	35.58	(z)-6-octadecenoic acid	level 1	[M+H-H2O]+	0.96		C08363	Lipids and lipid-like molecules	Fatty Acyls
M276T446	276.15	446.32	.gamma.-l-glu-.epsilon.-l-lys	level 1	[M+H]+	0.94	HMDB0003869	C21730	Organic acids and derivatives	Carboxylic acids and derivatives
M282T118	282.14	117.69	1-methyladenosine	level 1	[M+H]+	1.00	HMDB0003331	C02494	Nucleosides, nucleotides, and analogues	Purine nucleosides
M313T35	313.27	35.01	1-palmitoylglycerol	level 1	[M+H-H2O]+	0.96			Lipids and lipid-like molecules	Glycerolipids
M496T184	496.33	183.50	1-palmitoyl-sn-glycero-3-phosphocholine	level 1	[M+H]+	0.98	HMDB0010382		Lipids and lipid-like molecules	Glycerophospholipids
M747T37	746.55	36.57	1-stearoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine	level 1	[M+H]+	0.90	HMDB0008993		Lipids and lipid-like molecules	Glycerophospholipids
M341T35	341.30	34.66	1-stearoyl-rac-glycerol	level 1	[M+H-H2O]+	0.97			Lipids and lipid-like molecules	Glycerolipids
M716T32	715.61	32.08	1-Stearoyl-sn-glycerol	level 1	(2M-H)-	1.00				
M153T30_2	153.02	29.57	2,3-dihydroxybenzoic acid	level 1	[M-H]-	0.98	HMDB0000397	C00196	Benzenoids	Benzene and substituted derivatives
M117T137	117.05	137.31	2-methyl-3-hydroxybutyric acid	level 1	[M-H]-	0.92	HMDB0000354		Lipids and lipid-like molecules	Fatty Acyls
M181T344	181.01	343.87	3,4-dihydroxyhydrocinnamic acid	level 1	[M-H]-	0.77	HMDB0000423	C10447	Phenylpropanoids and polyketides	Phenylpropanoic acids
M104T326	104.07	325.75	3-aminobutanoic acid	level 1	[M+H]+	1.00	HMDB0031654		Organic acids and derivatives	Carboxylic acids and derivatives
M136T50	136.02	50.43	3-hydroxyanthranilic acid	level 1	[M+H-H2O]+	0.88	HMDB0001476	C00632	Benzenoids	Benzene and substituted derivatives
M146T367	146.09	366.96	4-Guanidinobutyric acid	level 1	(M+H)+	0.91	HMDB0003464	C01035	Organic acids and derivatives	Carboxylic acids and derivatives
M204T297	204.12	296.82	Acetylcarnitine	level 1	[M+H]+	1.00		C02571	Lipids and lipid-like molecules	Fatty Acyls
M146T368	146.12	367.61	Acetylcholine	level 1	[M]+	0.90	HMDB0000895	C01996	Organic nitrogen compounds	Organonitrogen compounds
M136T150	136.06	150.50	Adenine	level 1	[M+H]+	1.00	HMDB0000034	C00147	Organoheterocyclic compounds	Imidazopyrimidines
M268T158	268.10	157.92	Adenosine	level 1	[M+H]+	1.00	HMDB0000050	C00212	Nucleosides, nucleotides, and analogues	Purine nucleosides
M139T250	139.03	250.11	Allantoin	level 1	(M-H2O-H)-	0.88	HMDB0000462	C01551	Organoheterocyclic compounds	Azoles
M311T33	311.29	33.40	Arachidic acid	level 1	[M-H]-	0.99	HMDB0002212	C06425	Lipids and lipid-like molecules	Fatty Acyls
M246T407	246.15	406.61	Arg-Ala	level 1	[M+H]+	0.87			Organic acids and derivatives	Carboxylic acids and derivatives
M304T441	304.16	441.42	Arg-glu	level 1	[M+H]+	0.82			Organic acids and derivatives	Carboxylic acids and derivatives
M262T424	262.15	423.97	Arg-Ser	level 1	[M+H]+	0.98			Organic acids and derivatives	Carboxylic acids and derivatives
M274T369	274.18	369.01	Arg-Val	level 1	[M+H]+	0.87			Organic acids and derivatives	Carboxylic acids and derivatives
M187T346	187.10	346.05	Azelaic acid	level 1	[M-H]-	0.99	HMDB0000784	C08261	Lipids and lipid-like molecules	Fatty Acyls
M103T233	103.04	232.96	Beta-hydroxybutyrate	level 1	[M-H]-	0.93	HMDB0000011	C01089	Organic acids and derivatives	Hydroxy acids and derivatives

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M103T283	103.09	283.49	Betaine aldehyde	level 1	[M+H]+	0.80	HMDB0001252	C00576	Organic nitrogen compounds	Organonitrogen compounds
M380T34	380.35	34.12	C-6 ceramide	level 1	[M+H-H2O]+	0.99			Lipids and lipid-like molecules	Sphingolipids
M134T235	134.12	234.69	Caproic acid	level 1	(M+NH4)+	0.68	HMDB0000535/ HMDB0061883	C01585	Lipids and lipid-like molecules	Fatty Acyls
M393T34	393.28	33.61	Chenodeoxycholate	level 1	[M+H]+	0.77	HMDB0000518	C02528	Lipids and lipid-like molecules	Steroids and steroid derivatives
M465T26	465.30	25.63	Cholesteryl sulfate	level 1	[M-H]-	1.00	HMDB0000653	C18043	Lipids and lipid-like molecules	Steroids and steroid derivatives
M407T218	407.28	218.01	Cholic acid	level 1	[M-H]-	1.00	HMDB0000619	C00695	Lipids and lipid-like molecules	Steroids and steroid derivatives
M253T36_2	253.22	36.46	Cis-9-palmitoleic acid	level 1	[M-H]-	1.00	HMDB0003229	C08362	Lipids and lipid-like molecules	Fatty Acyls
M191T574	191.02	573.95	Citrate	level 1	(M-H)-	0.95	HMDB0000094	C00158	Organic acids and derivatives	Carboxylic acids and derivatives
M132T337	132.08	336.78	Creatine	level 1	[M+H]+	1.00	HMDB0000064	C00300	Organic acids and derivatives	Carboxylic acids and derivatives
M114T47	114.09	47.41	Creatinine	level 1	[M+H]+	0.77	HMDB0000562	C00791	Organic acids and derivatives	Carboxylic acids and derivatives
M112T187	112.05	187.46	Cytosine	level 1	[M+H]+	0.96	HMDB0000630	C00380	Organoheterocyclic compounds	Diazines
M161T388	161.04	388.04	D-Fructose	level 1	(M-H2O-H)-	0.65	HMDB0062538	C00095/ C05003/ C10906	Organooxygen compounds	Carbohydrates and carbohydrate conjugates
M241T78	241.00	77.68	D-glucose 6-phosphate	level 1	[M-H-H2O]-	0.95		C00092	Organic oxygen compounds	Organooxygen compounds
M177T156	177.06	156.36	D-Glucuronolactone	level 1	[M+H]+	0.85	HMDB0006355	C02670	Organoheterocyclic compounds	Lactones
M169T341	168.98	341.31	Dihydroxyacetone phosphate	level 1	[M-H]-	0.96	HMDB0001473	C00111	Organic oxygen compounds	Organooxygen compounds
M103T181	103.04	181.38	Dl-a-hydroxybutyric acid	level 1	[M-H]-	1.00	HMDB0000008	C05984	Organic acids and derivatives	Hydroxy acids and derivatives
M130T318	130.09	317.97	DL-arginine	level 1	[M+H-CH3ON]+	0.97	HMDB0000517/ HMDB0003416	C00792	Organic acids and derivatives	Carboxylic acids and derivatives
M89T224	89.02	224.38	Dl-lactate	level 1	[M-H]-	0.98	HMDB0001311/ HMDB0000190	C01432	Organic acids and derivatives	Hydroxy acids and derivatives
M166T266	166.11	266.34	DL-phenylalanine	level 1	[M+H]+	0.99		C02057	Organic acids and derivatives	Carboxylic acids and derivatives
M147T226	147.08	225.52	DL-Serine	level 1	(M+CH3CN+H)+	0.74	HMDB0003406/ HMDB0000187/ HMDB0062263	C00740/ C00065	Organic acids and derivatives	Carboxylic acids and derivatives
M149T87	149.06	86.99	D-lyxose	level 1	[M-H]-	0.98		C00476	Organic oxygen compounds	Organooxygen compounds
M341T388	341.11	388.16	D-Maltose	level 1	[M-H]-	0.98	HMDB0000163	C00208	Lipids and lipid-like molecules	Fatty Acyls
M217T30_1	217.02	30.20	D-Mannose	level 1	(M+K-2H)-	0.94	HMDB0000169	C00159	Organic oxygen compounds	Organooxygen compounds
M199T37	199.17	37.48	Dodecanoic acid	level 1	[M-H]-	1.00	HMDB0000638	C02679	Lipids and lipid-like molecules	Fatty Acyls
M133T173	133.09	173.48	D-ornithine	level 1	[M+H]+	0.73	HMDB0003374	C00515	Organic acids and derivatives	Carboxylic acids and derivatives
M455T30	455.11	30.15	Flavin mononucleotide (fmn)	level 1	[M-H]-	1.00	HMDB0001520	C00061	Nucleosides, nucleotides, and analogues	Flavin nucleotides
M474T246	474.18	246.19	Folinic acid	level 1	[M+H]+	0.98		C03479	Organic acids and derivatives	Carboxylic acids and derivatives
M259T250	259.01	249.97	Fructose 1-phosphate	level 1	[M-H]-	0.95	HMDB0001076	C01094	Organic oxygen compounds	Organooxygen compounds
M227T322	227.10	322.25	Glu-Pro	level 1	(M+H-H2O)+	0.68				

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M113T300	113.02	300.13	Glutaric acid	level 1	[M-H-H2O]-	0.96	HMDB0000661	C00489	Organic acids and derivatives	Carboxylic acids and derivatives
M232T463	232.14	462.54	Gly-Arg	level 1	(M+H)+	0.86			Organic acids and derivatives	Carboxylic acids and derivatives
M143T306	142.97	306.34	Glyceric acid	level 1	(M+K-2H)-	0.64	HMDB0000139/ HMDB0031818	C00258	Organic oxygen compounds	Organooxygen compounds
M285T35	285.24	35.14	Glycerol 1-myristate	level 1	[M+H-H2O]+	0.91			Lipids and lipid-like molecules	Glycerolipids
M171T384	171.00	383.71	Glycerol 3-phosphate	level 1	(M-H)-	1.00	HMDB0000126	C00093	Lipids and lipid-like molecules	Glycerophospholipids
M104T257_2	104.11	257.46	Glycerophosphocholine	level 1	[M+H-C3H7O5P]+	0.91	HMDB0000086	C00670	Lipids and lipid-like molecules	Glycerophospholipids
M269T36	269.25	35.60	Heptadecanoic acid	level 1	[M-H]-	1.00	HMDB0002259		Lipids and lipid-like molecules	Fatty Acyls
M306T250	306.08	250.03	His-Lys	level 1	[M+Na]+	1.00	HMDB0000133	C00387		
M319T247	319.13	246.95	His-Tyr	level 1	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M200T246	200.09	246.44	Homovanillic acid	level 1	(M+NH4)+	0.84	HMDB0000118	C05582	Benzenoids	Phenols
M181T181	181.05	180.86	Hydroxyphenyllactic acid	level 1	[M-H]-	0.95	HMDB0000755	C03672	Phenylpropanoids and polyketides	Phenylpropanoic acids
M135T159	135.03	158.75	Hypoxanthine	level 1	[M-H]-	0.99	HMDB0000157	C00262	Organoheterocyclic compounds	Imidazopyrimidines
M130T71	130.06	71.03	Indoleacetic acid	level 1	[M+H-CH2O2]+	0.99	HMDB0000197	C00954	Organoheterocyclic compounds	Indoles and derivatives
M212T29	212.00	28.94	Indoxyl sulfate	level 1	[M-H]-	0.99	HMDB0000682		Organic acids and derivatives	Organic sulfuric acids and derivatives
M267T210	267.07	210.37	Inosine	level 1	[M-H]-	0.99	HMDB0000195	C00294	Nucleosides, nucleotides, and analogues	Purine nucleosides
M365T379	365.10	378.78	Isomaltose	level 1	[M+Na]+	1.00	HMDB0002923	C00252	Lipids and lipid-like molecules	Fatty Acyls
M239T415	239.11	415.26	L-Anserine	level 1	(M-H)-	0.72	HMDB0000194	C01262	Organic acids and derivatives	Peptidomimetics
M175T546	175.12	545.69	L-Arginine	level 1	(M+H)+	0.99	HMDB0000517	C00062	Organic acids and derivatives	Carboxylic acids and derivatives
M132T488	132.03	487.76	L-Aspartate	level 1	(M-H)-	0.94	HMDB0000191	C00049	Organic acids and derivatives	Carboxylic acids and derivatives
M225T422	225.10	422.03	L-carnosine	level 1	[M-H]-	0.98	HMDB0000033	C00386	Organic acids and derivatives	Peptidomimetics
M198T386	198.08	386.24	L-citrulline	level 1	[M+Na]+	0.97	HMDB0000904	C00327	Organic acids and derivatives	Carboxylic acids and derivatives
M245T117	245.19	117.17	Leu-Leu	level 1	(M+H)+	1.00				
M165T145	165.07	145.49	L-fucitol	level 1	[M-H]-	0.73			Organic oxygen compounds	Organooxygen compounds
M243T217	243.02	217.05	L-fucose-1-phosphate	level 1	[M-H]-	0.71	HMDB0001265	C02985	Organic oxygen compounds	Organooxygen compounds
M181T294	181.07	293.59	L-iditol	level 1	[M-H]-	0.99	HMDB0011632	C01507	Organic oxygen compounds	Organooxygen compounds
M279T36	279.23	36.26	Linoleic acid	level 1	[M-H]-	1.00	HMDB0000673	C01595	Lipids and lipid-like molecules	Fatty Acyls
M400T147	400.35	146.97	L-Palmitoylcarnitine	level 1	(M+H)+	0.92	HMDB0000222	C02990	Lipids and lipid-like molecules	Fatty Acyls
M147T590	147.11	589.50	L-Pipecolic acid	level 1	(M+NH4)+	1.00	HMDB0000070/ HMDB0000716	C00408	Organic acids and derivatives	Carboxylic acids and derivatives
M128T302	128.03	302.35	L-pyroglutamic acid	level 1	[M-H]-	0.99	HMDB0000267	C01879	Organic acids and derivatives	Carboxylic acids and derivatives
M277T156	277.12	156.18	L-saccharopine	level 1	[M+H]+	1.00	HMDB0062698	C00449	Organic acids and derivatives	Carboxylic acids and derivatives

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M294T347	294.18	346.62	Lys-Phe	level 1	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M244T464	244.16	463.65	Lys-Pro	level 1	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M103T401	103.00	401.06	Malonic acid	level 1	(M-H)-	0.93	HMDB0000691	C00383	Organic acids and derivatives	Carboxylic acids and derivatives
M527T440	527.15	439.75	Maltotriose	level 1	[M+Na]+	1.00	HMDB0001262	C01835	Organic oxygen compounds	Organooxygen compounds
M117T389	117.02	389.10	Methylmalonic acid	level 1	[M-H]-	1.00	HMDB0000202	C02170	Organic acids and derivatives	Carboxylic acids and derivatives
M295T252	295.13	251.75	Mevalonic acid	level 1	[2M-H]-	0.76	HMDB0059629	C00418	Lipids and lipid-like molecules	Fatty Acyls
M227T36	227.20	36.03	Myristic acid	level 1	[M-H]-	1.00	HMDB0000806	C06424	Lipids and lipid-like molecules	Fatty Acyls
M300T250	300.04	250.10	N-Acetyl-D-Glucosamine 6-Phosphate	level 1	[M-H]-	0.71	HMDB0001367	C04256	Organic oxygen compounds	Organooxygen compounds
M187T313	187.07	312.87	N-acetylglutamine	level 1	[M-H]-	0.98	HMDB0006029		Organic acids and derivatives	Carboxylic acids and derivatives
M174T394	174.04	394.47	N-acetyl-l-aspartic acid	level 1	[M-H]-	0.98	HMDB0000812	C01042	Organic acids and derivatives	Carboxylic acids and derivatives
M188T390	188.06	390.39	N-acetyl-l-glutamate	level 1	[M-H]-	0.97	HMDB0001138	C00624	Organic acids and derivatives	Carboxylic acids and derivatives
M166T235	166.09	234.80	N-acetyl-l-phenylalanine	level 1	[M+H-C2H2O]+	0.99	HMDB0000512	C03519	Organic acids and derivatives	Carboxylic acids and derivatives
M308T372	308.10	371.82	N-acetylneuraminic acid	level 1	[M-H]-	1.00	HMDB0000230	C00270	Organic oxygen compounds	Organooxygen compounds
M131T314	131.12	314.38	N-acetylputrescine	level 1	[M+H]+	0.99	HMDB0002064	C02714	Organic acids and derivatives	Carboximidic acids and derivatives
M255T36	255.23	35.85	Palmitic acid	level 1	[M-H]-	1.00	HMDB0000220	C00249	Lipids and lipid-like molecules	Fatty Acyls
M204T65	204.12	65.38	Pantothenol	level 1	[M-H]-	0.91	HMDB0004231	C05944	Lipids and lipid-like molecules	Fatty Acyls
M195T121	195.05	121.25	Pectin (Galacturonic acid)	level 1	[M+H]+	1.00	HMDB0002545/ HMDB0003402	C08348	Organic oxygen compounds	Organooxygen compounds
M241T36	241.22	36.47	Pentadecanoic acid	level 1	[M-H]-	1.00	HMDB0000826	C16537	Lipids and lipid-like molecules	Fatty Acyls
M320T34	320.19	34.16	Phe-arg	level 1	[M-H]-	0.95			Organic acids and derivatives	Carboxylic acids and derivatives
M184T510	184.07	510.23	Phosphorylcholine	level 1	(M+H)+	0.99	HMDB0001565	C00588	Organic nitrogen compounds	Organonitrogen compounds
M210T192	210.08	191.50	Porphobilinogen	level 1	[M+H-NH3]+	0.79	HMDB0000245	C00931	Organic nitrogen compounds	Organonitrogen compounds
M299T75	299.30	75.30	Pristanic acid	level 1	[M+H]+	0.96	HMDB0000795		Lipids and lipid-like molecules	Prenol lipids
M247T360	247.14	359.93	Pro-Asn	level 1	(M+NH4)+	0.89				
M245T439	245.11	439.49	Pro-Glu	level 1	(M+H)+	0.96			Organic acids and derivatives	Carboxylic acids and derivatives
M302T57	302.30	56.95	Pro-Trp	level 1	[M+H]+	0.97	HMDB0000269	C00836	Organic nitrogen compounds	Organonitrogen compounds
M243T238	243.06	237.96	Pseudouridine	level 1	[M-H]-	0.74	HMDB0000767	C02067	Nucleosides, nucleotides, and analogues	Nucleoside and nucleotide analogues
M71T50	71.01	50.02	Pyruvaldehyde	level 1	[M-H]-	0.96	HMDB0001167	C00546	Organic oxygen compounds	Organooxygen compounds
M87T114	87.01	114.47	Pyruvate	level 1	[M-H]-	0.95	HMDB0000243	C00022	Organic acids and derivatives	Keto acids and derivatives
M133T186	133.05	186.01	Ribitol	level 1	(M-H2O-H)-	0.73	HMDB0000508	C00474	Organic oxygen compounds	Organooxygen compounds
M175T327	175.07	326.50	Ser-Ala	level 1	[M-H]-	0.84			Organic acids and derivatives	Carboxylic acids and derivatives

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M380T381	380.11	380.62	S-lactoylglutathione	level 1	[M+H]+	0.92	HMDB0001066	C03451	Organic acids and derivatives	Carboxylic acids and derivatives
M298T93	298.09	93.16	S-methyl-5'-thioadenosine	level 1	[M+H]+	1.00	HMDB0001173	C00170	Nucleosides, nucleotides, and analogues	5'-deoxyribonucleosides
M136T336	136.05	336.19	S-methyl-l-cysteine	level 1	[M+H]+	0.98	HMDB0002108	C22040	Organic acids and derivatives	Carboxylic acids and derivatives
M146T276	146.16	275.78	Spermidine	level 1	[M+H]+	1.00	HMDB0001257	C00315	Organic nitrogen compounds	Organonitrogen compounds
M300T35	300.29	35.49	Sphingosine	level 1	[M+H]+	0.96	HMDB0000252	C00319	Organic nitrogen compounds	Organonitrogen compounds
M117T93	117.02	92.59	Succinate	level 1	[M-H]-	0.91	HMDB0000254	C00042	Organic acids and derivatives	Carboxylic acids and derivatives
M124T292	124.01	291.97	Taurine	level 1	[M-H]-	1.00	HMDB0000251	C00245	Organic acids and derivatives	Organic sulfonic acids and derivatives
M265T220	265.12	220.35	Thr-Phe	level 1	[M-H]-	0.99			Organic acids and derivatives	Carboxylic acids and derivatives
M271T134	271.22	134.33	Trans-dehydroandrosterone	level 1	[M+H-H2O]+	0.89	HMDB0000077	C01227	Lipids and lipid-like molecules	Steroids and steroid derivatives
M117T444	117.10	444.24	Trimethylamine N-oxide	level 1	(M+CH3CN+H)+	0.99	HMDB0000925	C01104	Organic nitrogen compounds	Organonitrogen compounds
M334T247	334.13	246.96	Trp-Glu	level 1	[M+H]+	0.97			Organic acids and derivatives	Carboxylic acids and derivatives
M368T153	368.18	153.33	Trp-Tyr	level 1	[M+H]+	0.77			Organic acids and derivatives	Carboxylic acids and derivatives
M294T155	294.14	155.39	Tyr-Ala	level 1	(M+CH3CN+H)+	0.69				
M295T197	295.16	196.79	Tyr-Ile	level 1	[M+H]+	0.90			Organic acids and derivatives	Carboxylic acids and derivatives
M111T77	111.02	76.90	Uracil	level 1	[M-H]-	1.00	HMDB0000300	C00106	Organoheterocyclic compounds	Diazines
M61T94	61.04	94.14	Urea	level 1	[M+H]+	1.00	HMDB0000294	C00086	Organic acids and derivatives	Organic carbonic acids and derivatives
M243T148	243.06	147.75	Uridine	level 1	[M-H]-	0.92	HMDB0000296	C00299	Nucleosides, nucleotides, and analogues	Pyrimidine nucleosides
M137T330	137.03	330.38	Urocanic acid	level 1	(M-H)-	0.97	HMDB0000301/ HMDB0034174	C00785	Organoheterocyclic compounds	Azoles
M151T209	151.03	208.61	Xanthine	level 1	[M-H]-	0.96	HMDB0000292	C00385	Organoheterocyclic compounds	Imidazopyrimidines
M569T449	569.17	449.30	Xanthosine	level 1	[2M+H]+	0.93	HMDB0000299	C01762	Nucleosides, nucleotides, and analogues	Purine nucleosides
M250T26	250.14	26.31	[dala2] .alpha.-neoendorphin (1-2), amide	level 2	[M-H]-	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M793T136	792.57	136.31	1,2-dihexadecanoyl-sn-glycero-3-phosphocholine	level 2	[M+Hac-H]-	0.85	HMDB0000564	C00157	Lipids and lipid-like molecules	Glycerophospholipids
M699T30_2	699.47	29.82	1,2-dioleoyl-sn-glycero-3-phosphate	level 2	[M-H]-	0.97	HMDB0007865		Lipids and lipid-like molecules	Glycerophospholipids
M479T27	479.28	27.20	1.alpha.-methyl-5.alpha.-androstan-3.alpha.-ol-17-one glucuronide	level 2	[M-H]-	0.91				
M481T28_2	481.29	27.88	1.alpha.-methyl-5.alpha.-androstan-3.alpha.,17.beta.-diol glucuronide	level 2	[M-H]-	0.98				
M299T37	299.20	37.35	11-hydroxy-5z,8z,12e,14z,17z-eicosapentaenoic acid	level 2	[M-H-H2O]-	0.95			Lipids and lipid-like molecules	Fatty Acyls

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M271T36	271.22	35.78	16-hydroxyhexadecanoic acid	level 2	[M-H]-	0.84	HMDB0006294	C18218	Lipids and lipid-like molecules	Fatty Acyls
M377T28	377.23	28.06	16,16-dimethyl-6-ketoprostaglandin e1	level 2	[M-H-H2O]-	0.82			Lipids and lipid-like molecules	Fatty Acyls
M341T43	341.22	43.03	17-keto-4(z),7(z),10(z),13(z),15(e),19(z)-docosahexaenoic acid	level 2	[M-H]-	0.99			Lipids and lipid-like molecules	Fatty Acyls
M165T244	165.07	243.87	3-(4-hydroxyphenyl) propionic acid	level 2	[M-H]-	0.95	HMDB0002199	C01744		
M367T29	367.16	28.90	3-dehydroepiandrosterone sulfate	level 2	[M-H]-	0.73	HMDB0001032	C04555	Lipids and lipid-like molecules	Steroids and steroid derivatives
M503T451	503.16	450.68	3'-galactosyllactose	level 2	[M-H]-	0.93	HMDB0006599		Organic oxygen compounds	Organooxygen compounds
M635T63	635.45	63.30	5-Oxo-ETE	level 2	(2M-H)-	0.81				
M293T48	293.21	47.71	9-oxo-10(e),12(e)-octadecadienoic acid	level 2	[M-H]-	0.93			Lipids and lipid-like molecules	Fatty Acyls
M487T385	487.17	385.34	Blood group b trisaccharide	level 2	[M-H]-	0.76			Organic oxygen compounds	Organooxygen compounds
M133T33	132.99	33.37	Dl-malic acid	level 2	[M-H]-	0.73	HMDB0000744	C00497	Organic acids and derivatives	Hydroxy acids and derivatives
M309T37	309.28	36.70	Eicosenoic acid	level 2	[M-H]-	0.98		C16526	Lipids and lipid-like molecules	Fatty Acyls
M179T176	179.02	175.63	Glucose	level 2	[M-H]-	0.94	HMDB0000122	C00031	Organic oxygen compounds	Organooxygen compounds
M325T34	325.31	33.70	Heneicosanoic acid	level 2	[M-H]-	1.00	HMDB0002345		Lipids and lipid-like molecules	Fatty Acyls
M286T37	286.21	36.97	Hexadecanedioic acid	level 2	M-	0.69				
M130T268	130.09	268.47	Leucine	level 2	[M-H]-	0.78	HMDB0000687	C00123	Organic acids and derivatives	Carboxylic acids and derivatives
M377T387	377.08	386.51	Maltose	level 2	[M+Cl]-	0.77	HMDB0000163	C00208	Lipids and lipid-like molecules	Fatty Acyls
M300T145	300.04	145.30	N-acetyl-d-galactosamine 4-sulfate	level 2	[M-H]-	0.98			Organic oxygen compounds	Organooxygen compounds
M146T300	146.04	299.54	N-acetylserine	level 2	[M-H]-	0.84	HMDB0002931		Organic acids and derivatives	Carboxylic acids and derivatives
M374T32_2	374.25	32.09	N-arachidonoyl-l-alanine	level 2	[M-H]-	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M290T347	290.09	347.49	N-fructosyl pyroglutamate	level 2	[M-H]-	0.95			Organic acids and derivatives	Carboxylic acids and derivatives
M283T34	283.27	34.32	Octadecanoic acid	level 2	[M-H]-	1.00	HMDB0000827	C01530	Lipids and lipid-like molecules	Fatty Acyls
M695T30	695.31	29.97	S4:18(p3:16/f1:2)	level 2	[M+HCOO]-	0.94				
M762T177	761.58	177.36	Sm d34:1	level 2	[M+CH3COOH-H]-	1.00			Lipids and lipid-like molecules	Sphingolipids
M137T289	137.03	288.89	Urocanate	level 2	[M-H]-	0.99	HMDB0000301	C00785	Organoheterocyclic compounds	Azoles
M481T92	481.34	91.52	.beta.-ecdysone	level 2	[M+H]+	0.95	HMDB0030180	C02633	Lipids and lipid-like molecules	Steroids and steroid derivatives
M397T68	397.38	67.91	.beta.-sitosterol	level 2	[M+H-H2O]+	0.84	HMDB0000852	C01753	Lipids and lipid-like molecules	Steroids and steroid derivatives
M261T36	261.22	35.51	.gamma.-linolenoyl ethanolamide	level 2	[M+H-C2H7NO]+	0.81			Organic nitrogen compounds	Organonitrogen compounds
M362T65	362.32	64.94	(r)-(+)-arachidonyl-1'-hydroxy-2'-propylamide	level 2	[M+H]+	0.85			Lipids and lipid-like molecules	Fatty Acyls
M620T32	619.52	32.49	1-linoleoyl-2-oleoyl-rac-glycerol	level 2	[M+H]+	0.87			Lipids and lipid-like molecules	Fatty Acyls

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M355T35_1	355.28	34.95	1-monolinoleoyl-rac-glycerol	level 2	[M+H]+	0.84			Lipids and lipid-like molecules	Fatty Acyls
M733T37	732.54	36.71	1-oleoyl-2-myristoyl-sn-glycero-3-phosphocholine	level 2	[M+H]+	0.80	HMDB0008097		Lipids and lipid-like molecules	Glycerophospholipids
M505T286	505.23	286.07	1-stearoyl-2-hydroxy-sn-glycero-3-phosphate	level 2	[M-2H+3Na]+	1.00			Lipids and lipid-like molecules	Glycerophospholipids
M524T181	524.37	180.80	1-Stearoyl-sn-glycerol 3-phosphocholine(LPC(18:0))	level 2	[M+H]+	0.98	HMDB0010384	C04230	Lipids and lipid-like molecules	Glycerophospholipids
M608T33	607.56	32.93	1,2-dioctadecanoyl-sn-glycerol	level 2	[M+H-H2O]+	0.96	HMDB0007158		Lipids and lipid-like molecules	Glycerolipids
M381T35	381.29	35.44	1,24-dihydroxyvitamin d3	level 2	[M+H-2H2O]+	0.99		C12919	Lipids and lipid-like molecules	Steroids and steroid derivatives
M472T245	472.17	245.14	10-formyl-7,8-dihydrofolic acid	level 2	[M+H]+	0.98	HMDB0006485	C03204	Organoheterocyclic compounds	Pteridines and derivatives
M507T34	507.27	33.68	11.alpha.-hydroxyprogesterone .beta.-d-glucuronide	level 2	[M+H]+	1.00			Lipids and lipid-like molecules	Steroids and steroid derivatives
M289T40_1	289.16	40.16	2-hydroxyestradiol	level 2	[M+H]+	1.00	HMDB0000338	C05301	Lipids and lipid-like molecules	Steroids and steroid derivatives
M579T335	579.17	335.14	2-o-rhamnosylvitexin	level 2	[M+H]+	0.98		C12628	Phenylpropanoids and polyketides	Flavonoids
M143T51	143.11	51.37	2-octenoic acid, (e)-	level 2	[M+H]+	0.82	HMDB0001568		Lipids and lipid-like molecules	Fatty Acyls
M761T37	760.57	36.51	2-oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine	level 2	[M+H]+	0.98	HMDB0007972	C00157	Lipids and lipid-like molecules	Glycerophospholipids
M349T77	349.18	77.34	2,3-dinor-8-iso prostaglandin-f2.alpha.	level 2	[M+Na]+	1.00		C14794	Lipids and lipid-like molecules	Fatty Acyls
M116T234	116.11	234.26	3-dehydrocarnitine	level 2	[M+H-CO2]+	0.89	HMDB0012154	C02636	Organic acids and derivatives	Keto acids and derivatives
M248T310	248.15	309.68	3-hydroxybutyrylcarnitine	level 2	[M+H]+	1.00	HMDB0062735		Lipids and lipid-like molecules	Fatty Acyls
M606T494	605.79	493.87	3,3',5-triiodo-l-thyronine	level 2	[M+H-CH2O2]+	0.94	HMDB0000265	C02465	Organic acids and derivatives	Carboxylic acids and derivatives
M118T373	118.09	373.12	5-aminovaleric acid	level 2	[M+H]+	0.99	HMDB0003355	C00431	Organic acids and derivatives	Carboxylic acids and derivatives
M401T34	401.34	33.56	7.alpha.,27-dihydroxycholesterol	level 2	[M+H-H2O]+	0.98		C06341	Lipids and lipid-like molecules	Steroids and steroid derivatives
M348T452	348.07	452.00	Adenosine 5'-monophosphate	level 2	[M+H]+	1.00	HMDB0000045	C00020	Nucleosides, nucleotides, and analogues	Purine nucleotides
M464T335_2	464.10	334.84	Adenylosuccinic acid	level 2	[M+H]+	0.80	HMDB0000536	C03794	Nucleosides, nucleotides, and analogues	Purine nucleotides
M89T21	89.07	21.24	Alanine	level 2	[M+H]+	0.93	HMDB0062251	C00041	Organic acids and derivatives	Carboxylic acids and derivatives
M241T405	241.13	405.17	Anserine	level 2	[M+H]+	0.94	HMDB0000194	C01262	Organic acids and derivatives	Peptidomimetics
M459T298	459.30	298.03	Arg-Arg-Lys	level 2	[M+H]+	0.71			Organic acids and derivatives	Carboxylic acids and derivatives
M232T427	232.14	427.16	Arg-gly	level 2	[M+H]+	0.99			Organic acids and derivatives	Carboxylic acids and derivatives
M272T441	272.17	441.44	Arg-Pro	level 2	[M+H]+	0.99			Organic acids and derivatives	Carboxylic acids and derivatives
M428T50	428.28	50.28	Arg-Pro-Arg	level 2	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M475T228	475.25	228.12	Asn-Trp-Arg	level 2	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M248T420	248.09	420.29	Asp-Asn	level 2	[M+H]+	0.96			Organic acids and derivatives	Carboxylic acids and derivatives

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M310T169	310.18	168.98	2-Methylbutyroyl-carnitine	level 2	(M+CH3CN+Na)+	0.98				
M552T411	552.18	411.26	Blood group a trisaccharide	level 2	[M+Na]+	1.00			Organic oxygen compounds	Organooxygen compounds
M288T38	288.29	37.92	C17-sphinganine	level 2	[M+H]+	0.75			Organic nitrogen compounds	Organonitrogen compounds
M321T34	321.31	33.63	Cis-13-docosenoic acid	level 2	[M+H-H2O]+	0.99	HMDB0002068	C08316	Lipids and lipid-like molecules	Fatty Acyls
M351T34	351.18	33.70	Cys-Thr-Lys	level 2	[M+H]+	0.72			Organic acids and derivatives	Carboxylic acids and derivatives
M147T420	147.08	419.85	D-glutamine	level 2	[M+H]+	1.00	HMDB0003423	C00064	Organic acids and derivatives	Carboxylic acids and derivatives
M160T375	160.13	374.74	Dl-2-aminocaprylic acid	level 2	[M+H]+	0.98	HMDB0000991		Organic acids and derivatives	Carboxylic acids and derivatives
M145T369	145.10	369.04	Dl-5-hydroxylysine	level 2	[M+H-H2O]+	0.95			Organic acids and derivatives	Carboxylic acids and derivatives
M148T390	148.06	389.88	DL-Glutamic acid	level 2	[M+H]+	0.97	HMDB0060475	C00025	Organic acids and derivatives	Carboxylic acids and derivatives
M147T369	147.08	369.37	DL-glutamine	level 2	[M+H]+	1.00		C00303	Organic acids and derivatives	Carboxylic acids and derivatives
M116T308	116.07	307.87	DL-proline	level 2	[M+H]+	1.00	HMDB0000162	C00148	Organic acids and derivatives	Carboxylic acids and derivatives
M188T191	188.07	191.06	DL-tryptophan	level 2	[M+H-NH3]+	0.97	HMDB0030396	C00078	Organoheterocyclic compounds	Indoles and derivatives
M281T35_1	281.10	34.62	5-methyluridine	level 2	[M+Na]+	0.75	HMDB0000884			
M146T347	146.09	346.52	G-guanidinobutyrate	level 2	[M+H]+	0.94	HMDB0003464	C01035	Organic acids and derivatives	Carboxylic acids and derivatives
M406T365	406.13	365.08	Galacto-n-biose	level 2	[M+Na]+	0.94		C07278	Organic oxygen compounds	Organooxygen compounds
M244T356	244.13	356.21	Gln-pro	level 2	[M+H]+	0.91	HMDB0028805		Organic acids and derivatives	Carboxylic acids and derivatives
M333T34	333.17	33.71	Gly-Glu-Lys	level 2	[M+H]+	0.73			Organic acids and derivatives	Carboxylic acids and derivatives
M288T59	288.29	58.58	Heptadecasphinganine	level 2	[M+H]+	0.97			Organic nitrogen compounds	Organonitrogen compounds
M257T35_1	257.25	34.90	Hexadecanoic acid	level 2	[M+H]+	0.94	HMDB0000220	C00249	Lipids and lipid-like molecules	Fatty Acyls
M260T214	260.18	214.02	Hexanoyl-l-carnitine	level 2	[M+H]+	1.00	HMDB0000756		Lipids and lipid-like molecules	Fatty Acyls
M232T247	232.15	247.02	Isobutyryl-l-carnitine	level 2	[M+H]+	1.00	HMDB0000736		Lipids and lipid-like molecules	Fatty Acyls
M285T160	285.29	160.03	Isostearic acid	level 2	[M+H]+	0.90	HMDB0031066	C20356	Lipids and lipid-like molecules	Fatty Acyls
M246T231	246.17	231.07	Isovaleryl-l-carnitine	level 2	[M+H]+	1.00			Lipids and lipid-like molecules	Fatty Acyls
M144T530	144.10	530.01	L-homoarginine	level 2	[M+H-CH3ON]+	0.76	HMDB0000670	C01924	Organic acids and derivatives	Carboxylic acids and derivatives
M190T388	190.11	387.68	L-homocitrulline	level 2	[M+H]+	0.95	HMDB0000679	C02427	Organic acids and derivatives	Carboxylic acids and derivatives
M116T272	116.08	272.46	L-hydroxyarginine	level 2	[M+H-CH5ON3]+	1.00	HMDB0004224	C05933	Organic acids and derivatives	Carboxylic acids and derivatives
M218T269	218.14	269.14	L-propionylcarnitine	level 2	[M+H]+	1.00	HMDB0062514		Lipids and lipid-like molecules	Fatty Acyls
M365T416	365.10	415.65	Lactose	level 2	[M+Na]+	1.00	HMDB0000186	C00243	Organic oxygen compounds	Organooxygen compounds
M245T173	245.18	172.94	Leucylleucine	level 2	[M+H]+	0.86	HMDB0028933	C11332	Organic acids and derivatives	Carboxylic acids and derivatives
M569T107	569.31	107.21	Leukotriene f4	level 2	[M+H]+	1.00		C06462	Lipids and lipid-like molecules	Fatty Acyls

ID	m/z	rt(s)	Name	MSI Level	adduct	score	HMDB	KEGG	SuperClass	Class
M218T425	218.15	424.79	Lys-Ala	level 2	[M+H]+	0.99			Organic acids and derivatives	Carboxylic acids and derivatives
M130T80	130.08	80.40	Lysine	level 2	[M+H-NH3]+	1.00	HMDB0000182	C00047	Organic acids and derivatives	Carboxylic acids and derivatives
M377T38	377.21	38.38	Met-Val-Lys	level 2	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M157T284	157.10	284.18	N-.alpha.-acetyl-l-ornithine	level 2	[M+H-H2O]+	1.00	HMDB0003357	C00437	Organic acids and derivatives	Carboxylic acids and derivatives
M350T35	350.30	35.04	N-(8z,11z,14z-eicosatrienoyl) ethanolamine	level 2	[M+H]+	0.73	HMDB0013625		Organic nitrogen compounds	Organonitrogen compounds
M595T32	594.58	32.18	N-(eicosanoyl) sphingosine	level 2	[M+H]+	0.96	HMDB0004951		Lipids and lipid-like molecules	Sphingolipids
M238T156	238.11	155.86	N-(phenylacetyl)-l-phenylalanine	level 2	[M+H-CH2O2]+	0.95	HMDB0002372		Organic acids and derivatives	Carboxylic acids and derivatives
M160T395	160.10	394.59	N-acetyl-dl-valine	level 2	[M+H]+	0.90	HMDB0011757		Organic acids and derivatives	Carboxylic acids and derivatives
M198T309	198.09	309.34	N-acetylhistidine	level 2	[M+H]+	0.93	HMDB0014748	C02997	Organic acids and derivatives	Carboxylic acids and derivatives
M310T155	310.13	154.54	N-acetylneuraminate	level 2	[M+H]+	0.90	HMDB0000230	C00270	Organic oxygen compounds	Organooxygen compounds
M123T59	123.05	59.22	Niacinamide	level 2	[M+H]+	1.00	HMDB0001406	C00153	Organoheterocyclic compounds	Pyridines and derivatives
M282T34	282.28	34.26	Oleamide	level 2	[M+H]+	0.96	HMDB0002117	C19670	Lipids and lipid-like molecules	Fatty Acyls
M202T52	202.11	52.15	Pantothenic acid	level 2	[M+H-H2O]+	0.89	HMDB0000210	C00864	Organic acids and derivatives	Carboxylic acids and derivatives
M181T61	181.07	60.62	Paraxanthine	level 2	[M+H]+	0.99	HMDB0001860	C13747	Organoheterocyclic compounds	Imidazopyrimidines
M166T263	166.08	263.33	Phenylalanine	level 2	[M+H]+	1.00	HMDB0000159	C00079	Organic acids and derivatives	Carboxylic acids and derivatives
M194T138	194.12	137.83	Pro-Asp-Arg	level 2	[M+2H]2+	0.76			Organic acids and derivatives	Carboxylic acids and derivatives
M229T359	229.15	358.69	Pro-leu	level 2	[M+H]+	0.88			Organic acids and derivatives	Carboxylic acids and derivatives
M213T410	213.12	410.01	Pro-pro	level 2	[M+H]+	1.00			Organic acids and derivatives	Carboxylic acids and derivatives
M720T507	720.39	507.42	Progesterone 3-biotin	level 2	[M+Na]+	0.81			Lipids and lipid-like molecules	Steroids and steroid derivatives
M399T133	399.16	133.39	S-adenosyl-l-methionine	level 2	[M+H]+	0.98	HMDB0001185	C00019	Nucleosides, nucleotides, and analogues	5'-deoxyribonucleosides
M294T35	294.24	35.46	Stearidonic Acid	level 2	(M+NH4)+	0.67				
M159T269	159.11	268.72	Val-Ala-Lys	level 2	[M+2H]2+	0.82			Organic acids and derivatives	Carboxylic acids and derivatives
M194T258	194.14	258.47	Val-Leu-Arg	level 2	[M+2H]2+	0.71			Organic acids and derivatives	Carboxylic acids and derivatives

Table S2. KEGG enrichment of lower airway metabolite clusters.

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
cluster 1	Regulation of actin cyto-skeleton	1	21	5	4491	0.05	0.00	Over	0.02	0.12	0.20	M146T368
	ABC transporters	3	21	138	4491	0.14	0.03	Over	0.03	0.12	0.02	M365T416;M569T449;M527T440
	cGMP-PKG signaling pathway	1	21	10	4491	0.05	0.00	Over	0.05	0.13	0.10	M348T452
	cAMP signaling pathway	3	21	25	4491	0.14	0.01	Over	0.00	0.01	0.12	M348T452;M103T233;M87T361;M146T368
	FoxO signaling pathway	1	21	5	4491	0.05	0.00	Over	0.02	0.12	0.20	M348T452
	mTOR signaling pathway	1	21	4	4491	0.05	0.00	Over	0.02	0.12	0.25	M348T452
	PI3K-Akt signaling pathway	1	21	4	4491	0.05	0.00	Over	0.02	0.12	0.25	M348T452
	AMPK signaling pathway	1	21	22	4491	0.05	0.00	Over	0.10	0.16	0.05	M348T452
	Neuroactive ligand-receptor interaction	2	21	53	4491	0.10	0.01	Over	0.02	0.12	0.04	M146T368;M606T494
	Aminoacyl-tRNA biosynthesis	1	21	52	4491	0.05	0.01	Over	0.22	0.26	0.02	M188T191
	Central carbon metabolism in cancer	1	21	37	4491	0.05	0.01	Over	0.16	0.22	0.03	M188T191
	Antifolate resistance	1	21	17	4491	0.05	0.00	Over	0.08	0.14	0.06	M348T452
	Cushing syndrome	1	21	13	4491	0.05	0.00	Over	0.06	0.13	0.08	M348T452
	Autoimmune thyroid disease	1	21	3	4491	0.05	0.00	Over	0.01	0.12	0.33	M606T494
	African trypanosomiasis	1	21	8	4491	0.05	0.00	Over	0.04	0.13	0.13	M188T191
	Parkinson disease	1	21	26	4491	0.05	0.01	Over	0.12	0.18	0.04	M348T452
	Pathways of neurodegenera-tion - multiple diseases	2	21	32	4491	0.10	0.01	Over	0.01	0.12	0.06	M348T452;M146T368
	Morphine addiction	1	21	8	4491	0.05	0.00	Over	0.04	0.13	0.13	M348T452
	Nicotine addiction	1	21	7	4491	0.05	0.00	Over	0.03	0.13	0.14	M146T368
	Arginine biosynthesis	1	21	23	4491	0.05	0.01	Over	0.10	0.16	0.04	M198T386
	Alanine, aspartate and gluta-mate metabolism	1	21	28	4491	0.05	0.01	Over	0.12	0.18	0.04	M464T335_2
	Glycine, serine and threonine metabolism	1	21	48	4491	0.05	0.01	Over	0.20	0.25	0.02	M188T191
	Cysteine and methionine metabolism	1	21	68	4491	0.05	0.02	Over	0.27	0.31	0.01	M298T93
	Lysine degradation	1	21	56	4491	0.05	0.01	Over	0.23	0.27	0.02	M118T373
	Arginine and proline me-tabolism	2	21	71	4491	0.10	0.02	Over	0.04	0.13	0.03	M118T373;M146T367
	Tyrosine metabolism	1	21	78	4491	0.05	0.02	Over	0.31	0.34	0.01	M606T494
	Tryptophan metabolism	2	21	83	4491	0.10	0.02	Over	0.06	0.13	0.02	M188T191;M136T50
	Phenylalanine, tyrosine and tryptophan biosynthesis	1	21	35	4491	0.05	0.01	Over	0.15	0.21	0.03	M188T191
	Caffeine metabolism	1	21	22	4491	0.05	0.00	Over	0.10	0.16	0.05	M569T449
	Pentose and glucuronate interconversions	1	21	59	4491	0.05	0.01	Over	0.24	0.27	0.02	M149T87
	Galactose metabolism	1	21	46	4491	0.05	0.01	Over	0.19	0.25	0.02	M365T416
	Amino sugar and nucleotide sugar metabolism	1	21	119	4491	0.05	0.03	Over	0.43	0.46	0.01	M310T155
	Butanoate metabolism	1	21	47	4491	0.05	0.01	Over	0.20	0.25	0.02	M103T233;M87T361
	Metabolic pathways	16	21	3101	4491	0.76	0.69	Over	0.33	0.35	0.01	M348T452;M188T191;M298T93;M365T416;M310T155;M198T386;M118T373;M136T50;M130T318;M210T192;M146T367;M103T233;M87T361;M569T449;M606T494;M474T246;M464T335_2
	2-Oxocarboxylic acid metabolism	1	21	144	4491	0.05	0.03	Over	0.50	0.51	0.01	M188T191
	Fatty acid metabolism	1	21	122	4491	0.05	0.03	Over	0.44	0.46	0.01	M400T147
	Biosynthesis of amino acids	2	21	128	4491	0.10	0.03	Over	0.12	0.18	0.02	M188T191;M198T386
	Nucleotide metabolism	3	21	58	4491	0.14	0.01	Over	0.00	0.08	0.05	M348T452;M569T449;M464T335_2
	Biosynthesis of cofactors	5	21	328	4491	0.24	0.07	Over	0.02	0.12	0.02	M348T452;M188T191;M136T50;M210T192;M464T335_2
	Biosynthesis of nucleotide sugars	1	21	200	4491	0.05	0.04	Over	0.62	0.62	0.01	M310T155
	Fatty acid degradation	1	21	50	4491	0.05	0.01	Over	0.21	0.25	0.02	M400T147

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Primary bile acid biosynthesis	1	21	47	4491	0.05	0.01	Over	0.20	0.25	0.02	M401T34
	Glycerophospholipid metabolism	1	21	56	4491	0.05	0.01	Over	0.23	0.27	0.02	M146T368
	One carbon pool by folate	1	21	9	4491	0.05	0.00	Over	0.04	0.13	0.11	M474T246
	Porphyrin metabolism	1	21	148	4491	0.05	0.03	Over	0.51	0.51	0.01	M210T192
	D-Amino acid metabolism	2	21	69	4491	0.10	0.02	Over	0.04	0.13	0.03	M118T373;M130T318
	Purine metabolism	3	21	101	4491	0.14	0.02	Over	0.01	0.12	0.03	M348T452;M569T449;M464T335_2
	Longevity regulating pathway	1	21	8	4491	0.05	0.00	Over	0.04	0.13	0.13	M348T452
	Salivary secretion	1	21	17	4491	0.05	0.00	Over	0.08	0.14	0.06	M146T368
	Gastric acid secretion	1	21	14	4491	0.05	0.00	Over	0.06	0.13	0.07	M146T368
	Pancreatic secretion	1	21	15	4491	0.05	0.00	Over	0.07	0.14	0.07	M146T368
	Carbohydrate digestion and absorption	2	21	27	4491	0.10	0.01	Over	0.01	0.12	0.07	M365T416;M527T440
	Protein digestion and absorption	1	21	47	4491	0.05	0.01	Over	0.20	0.25	0.02	M188T191
	Bile secretion	2	21	97	4491	0.10	0.02	Over	0.07	0.14	0.02	M146T368;M606T494
	Mineral absorption	1	21	29	4491	0.05	0.01	Over	0.13	0.18	0.03	M188T191
	Insulin secretion	1	21	12	4491	0.05	0.00	Over	0.05	0.13	0.08	M146T368
	Thyroid hormone synthesis	1	21	21	4491	0.05	0.00	Over	0.09	0.16	0.05	M606T494
	Thyroid hormone signaling pathway	1	21	11	4491	0.05	0.00	Over	0.05	0.13	0.09	M606T494
	Regulation of lipolysis in adipocytes	1	21	14	4491	0.05	0.00	Over	0.06	0.13	0.07	M348T452
	Renin secretion	1	21	17	4491	0.05	0.00	Over	0.08	0.14	0.06	M348T452
	Aldosterone synthesis and secretion	1	21	22	4491	0.05	0.00	Over	0.10	0.16	0.05	M348T452
	Cortisol synthesis and secretion	1	21	12	4491	0.05	0.00	Over	0.05	0.13	0.08	M348T452
	Parathyroid hormone synthesis, secretion and action	1	21	11	4491	0.05	0.00	Over	0.05	0.13	0.09	M348T452
	Thermogenesis	1	21	23	4491	0.05	0.01	Over	0.10	0.16	0.04	M606T494
	Synaptic vesicle cycle	1	21	12	4491	0.05	0.00	Over	0.05	0.13	0.08	M146T368
	Cholinergic synapse	1	21	12	4491	0.05	0.00	Over	0.05	0.13	0.08	M146T368
	Serotonergic synapse	1	21	42	4491	0.05	0.01	Over	0.18	0.24	0.02	M188T191
	Olfactory transduction	1	21	8	4491	0.05	0.00	Over	0.04	0.13	0.13	M348T452
	Taste transduction	2	21	32	4491	0.10	0.01	Over	0.01	0.12	0.06	M348T452;M146T368
cluster 2	Apoptosis	1	26	4	4491	0.04	0.00	Over	0.02	0.13	0.25	M300T35
	Ferroptosis	1	26	29	4491	0.04	0.01	Over	0.16	0.22	0.03	M148T390
	Necroptosis	1	26	10	4491	0.04	0.00	Over	0.06	0.13	0.10	M300T35
	Gap junction	1	26	11	4491	0.04	0.00	Over	0.06	0.13	0.09	M148T390
	Efferocytosis	1	26	21	4491	0.04	0.00	Over	0.12	0.19	0.05	M524T181
	ABC transporters	4	26	138	4491	0.15	0.03	Over	0.01	0.06	0.03	M148T390;M268T158;M306T250;M136T336
	cGMP-PKG signaling pathway	1	26	10	4491	0.04	0.00	Over	0.06	0.13	0.10	M268T158
	cAMP signaling pathway	1	26	25	4491	0.04	0.01	Over	0.14	0.20	0.04	M268T158
	FoxO signaling pathway	1	26	5	4491	0.04	0.00	Over	0.03	0.13	0.20	M148T390
	Sphingolipid signaling pathway	3	26	15	4491	0.12	0.00	Over	0.00	0.00	0.20	M268T158;M300T35;M302T57
	Phospholipase D signaling pathway	1	26	11	4491	0.04	0.00	Over	0.06	0.13	0.09	M148T390
	Neuroactive ligand-receptor interaction	2	26	53	4491	0.08	0.01	Over	0.04	0.13	0.04	M148T390;M268T158
	Aminoacyl-tRNA biosynthesis	1	26	52	4491	0.04	0.01	Over	0.26	0.29	0.02	M148T390
	Central carbon metabolism in cancer	1	26	37	4491	0.04	0.01	Over	0.19	0.25	0.03	M148T390
	Choline metabolism in cancer	3	26	11	4491	0.12	0.00	Over	0.00	0.00	0.27	M761T37;M104T257_2;M524T181
	Insulin resistance	1	26	19	4491	0.04	0.00	Over	0.10	0.18	0.05	M204T297
	Parkinson disease	1	26	26	4491	0.04	0.01	Over	0.14	0.21	0.04	M268T158

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Amyotrophic lateral sclerosis	1	26	14	4491	0.04	0.00	Over	0.08	0.15	0.07	M148T390
	Huntington disease	1	26	6	4491	0.04	0.00	Over	0.03	0.13	0.17	M148T390
	Spinocerebellar ataxia	1	26	7	4491	0.04	0.00	Over	0.04	0.13	0.14	M148T390
	Pathways of neurodegeneration - multiple diseases	1	26	32	4491	0.04	0.01	Over	0.17	0.22	0.03	M148T390
	Cocaine addiction	1	26	7	4491	0.04	0.00	Over	0.04	0.13	0.14	M148T390
	Amphetamine addiction	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Morphine addiction	1	26	8	4491	0.04	0.00	Over	0.05	0.13	0.13	M268T158
	Nicotine addiction	1	26	7	4491	0.04	0.00	Over	0.04	0.13	0.14	M148T390
	Alcoholism	2	26	10	4491	0.08	0.00	Over	0.00	0.03	0.20	M148T390;M268T158
	Arginine biosynthesis	2	26	23	4491	0.08	0.01	Over	0.01	0.06	0.09	M148T390;M157T284
	Alanine, aspartate and glutamate metabolism	1	26	28	4491	0.04	0.01	Over	0.15	0.22	0.04	M148T390
	Glycine, serine and threonine metabolism	2	26	48	4491	0.08	0.01	Over	0.03	0.13	0.04	M132T337;M103T283
	Arginine and proline metabolism	2	26	71	4491	0.08	0.02	Over	0.06	0.13	0.03	M148T390;M132T337
	Histidine metabolism	3	26	47	4491	0.12	0.01	Over	0.00	0.03	0.06	M148T390;M137T330;M239T415;M241T405
	Phenylalanine metabolism	1	26	49	4491	0.04	0.01	Over	0.25	0.28	0.02	M166T235
	Neomycin, kanamycin and gentamicin biosynthesis	1	26	81	4491	0.04	0.02	Over	0.38	0.39	0.01	M148T390
	Glyoxylate and dicarboxylate metabolism	1	26	64	4491	0.04	0.01	Over	0.31	0.34	0.02	M148T390
	Butanoate metabolism	1	26	47	4491	0.04	0.01	Over	0.24	0.28	0.02	M148T390
	Nitrogen metabolism	1	26	20	4491	0.04	0.00	Over	0.11	0.18	0.05	M148T390
	Metabolic pathways	22	26	3101	4491	0.85	0.69	Over	0.06	0.13	0.01	M148T390;M111T77;M136T150;M123T59;M761T37;M268T158;M135T159;M132T337;M300T35;M112T187;M306T250;M157T284;M103T283;M407T218;M137T330;M302T57;M239T415;M241T405;M165T244;M393T34;M166T235;M227T36;M253T36_2
	Carbon metabolism	1	26	112	4491	0.04	0.02	Over	0.48	0.50	0.01	M148T390
	2-Oxocarboxylic acid metabolism	2	26	144	4491	0.08	0.03	Over	0.20	0.25	0.01	M148T390;M157T284
	Biosynthesis of amino acids	2	26	128	4491	0.08	0.03	Over	0.17	0.22	0.02	M148T390;M157T284
	Nucleotide metabolism	6	26	58	4491	0.23	0.01	Over	0.00	0.00	0.10	M111T77;M136T150;M268T158;M135T159;M112T187;M306T250
	Biosynthesis of cofactors	2	26	328	4491	0.08	0.07	Over	0.58	0.58	0.01	M148T390;M123T59
	Fatty acid biosynthesis	2	26	58	4491	0.08	0.01	Over	0.04	0.13	0.03	M227T36;M253T36_2
	Primary bile acid biosynthesis	2	26	47	4491	0.08	0.01	Over	0.03	0.13	0.04	M407T218;M393T34
	Glycerophospholipid metabolism	3	26	56	4491	0.12	0.01	Over	0.00	0.04	0.05	M761T37;M104T257_2;M524T181
	Ether lipid metabolism	1	26	25	4491	0.04	0.01	Over	0.14	0.20	0.04	M104T257_2
	Arachidonic acid metabolism	1	26	79	4491	0.04	0.02	Over	0.37	0.39	0.01	M761T37
	Linoleic acid metabolism	1	26	29	4491	0.04	0.01	Over	0.16	0.22	0.03	M761T37
	alpha-Linolenic acid metabolism	1	26	44	4491	0.04	0.01	Over	0.23	0.27	0.02	M761T37
	Sphingolipid metabolism	2	26	35	4491	0.08	0.01	Over	0.02	0.11	0.06	M300T35;M302T57
	Nicotinate and nicotinamide metabolism	1	26	55	4491	0.04	0.01	Over	0.27	0.30	0.02	M123T59
	Pantothenate and CoA biosynthesis	1	26	30	4491	0.04	0.01	Over	0.16	0.22	0.03	M111T77
	Porphyrin metabolism	1	26	148	4491	0.04	0.03	Over	0.58	0.58	0.01	M148T390
	beta-Alanine metabolism	2	26	32	4491	0.08	0.01	Over	0.01	0.10	0.06	M111T77;M239T415;M241T405
	Taurine and hypotaurine metabolism	1	26	24	4491	0.04	0.01	Over	0.13	0.20	0.04	M148T390
	D-Amino acid metabolism	1	26	69	4491	0.04	0.02	Over	0.33	0.36	0.01	M148T390
	Glutathione metabolism	1	26	38	4491	0.04	0.01	Over	0.20	0.25	0.03	M148T390
	Purine metabolism	4	26	101	4491	0.15	0.02	Over	0.00	0.03	0.04	M136T150;M268T158;M135T159;M306T250
	Pyrimidine metabolism	2	26	66	4491	0.08	0.01	Over	0.06	0.13	0.03	M111T77;M112T187

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Vascular smooth muscle contraction	1	26	16	4491	0.04	0.00	Over	0.09	0.16	0.06	M268T158
	Protein digestion and absorption	1	26	47	4491	0.04	0.01	Over	0.24	0.28	0.02	M148T390
	Bile secretion	2	26	97	4491	0.08	0.02	Over	0.11	0.18	0.02	M407T218;M393T34
	Vitamin digestion and absorption	1	26	42	4491	0.04	0.01	Over	0.22	0.26	0.02	M123T59
	Regulation of lipolysis in adipocytes	1	26	14	4491	0.04	0.00	Over	0.08	0.15	0.07	M268T158
	Renin secretion	1	26	17	4491	0.04	0.00	Over	0.09	0.17	0.06	M268T158
	Circadian entrainment	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Proximal tubule bicarbonate reclamation	1	26	17	4491	0.04	0.00	Over	0.09	0.17	0.06	M148T390
	Long-term potentiation	1	26	7	4491	0.04	0.00	Over	0.04	0.13	0.14	M148T390
	Synaptic vesicle cycle	1	26	12	4491	0.04	0.00	Over	0.07	0.13	0.08	M148T390
	Retrograde endocannabinoid signaling	2	26	19	4491	0.08	0.00	Over	0.01	0.05	0.11	M148T390;M761T37
	Glutamatergic synapse	1	26	8	4491	0.04	0.00	Over	0.05	0.13	0.13	M148T390
	GABAergic synapse	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Long-term depression	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Taste transduction	1	26	32	4491	0.04	0.01	Over	0.17	0.22	0.03	M148T390
cluster 3	Ferroptosis	1	34	29	4491	0.03	0.01	Over	0.20	0.25	0.03	M295T252
	Lysosome	1	34	4	4491	0.03	0.00	Over	0.03	0.09	0.25	M217T30_1
	Efferocytosis	2	34	21	4491	0.06	0.00	Over	0.01	0.04	0.10	M179T176;M175T546
	ABC transporters	9	34	138	4491	0.26	0.03	Over	0.00	0.00	0.07	M179T176;M89T21;M132T488;M175T546;M147T420;M130T268;M217T30_1;M267T210;M146T276
	HIF-1 signaling pathway	1	34	15	4491	0.03	0.00	Over	0.11	0.18	0.07	M179T176
	FoxO signaling pathway	1	34	5	4491	0.03	0.00	Over	0.04	0.10	0.20	M179T176
	mTOR signaling pathway	2	34	4	4491	0.06	0.00	Over	0.00	0.00	0.50	M175T546;M130T268
	AMPK signaling pathway	1	34	22	4491	0.03	0.00	Over	0.15	0.22	0.05	M179T176
	Neuroactive ligand-receptor interaction	1	34	53	4491	0.03	0.01	Over	0.33	0.37	0.02	M132T488
	Sulfur relay system	1	34	11	4491	0.03	0.00	Over	0.08	0.15	0.09	M89T21
	Aminoacyl-tRNA biosynthesis	5	34	52	4491	0.15	0.01	Over	0.00	0.00	0.10	M89T21;M132T488;M175T546;M147T420;M130T268
	Chemical carcinogenesis - reactive oxygen species	1	34	57	4491	0.03	0.01	Over	0.35	0.39	0.02	M289T40_1
	Central carbon metabolism in cancer	8	34	37	4491	0.24	0.01	Over	0.00	0.00	0.22	M179T176;M89T21;M132T488;M175T546;M147T420;M241T78;M130T268;M191T574
	Choline metabolism in cancer	1	34	11	4491	0.03	0.00	Over	0.08	0.15	0.09	M793T136
	Diabetic cardiomyopathy	3	34	39	4491	0.09	0.01	Over	0.00	0.02	0.08	M179T176;M241T78;M71T50
	Type II diabetes mellitus	1	34	6	4491	0.03	0.00	Over	0.04	0.11	0.17	M179T176
	Insulin resistance	2	34	19	4491	0.06	0.00	Over	0.01	0.04	0.11	M179T176;M241T78
	Non-alcoholic fatty liver disease	1	34	2	4491	0.03	0.00	Over	0.02	0.06	0.50	M179T176
	AGE-RAGE signaling pathway in diabetic complications	1	34	9	4491	0.03	0.00	Over	0.07	0.13	0.11	M179T176
	Shigellosis	1	34	14	4491	0.03	0.00	Over	0.10	0.17	0.07	M130T268
	Chagas disease	1	34	6	4491	0.03	0.00	Over	0.04	0.11	0.17	M175T546
	Amoebiasis	1	34	13	4491	0.03	0.00	Over	0.09	0.16	0.08	M175T546
	Amyotrophic lateral sclerosis	1	34	14	4491	0.03	0.00	Over	0.10	0.17	0.07	M175T546
	Pathways of neurodegeneration - multiple diseases	1	34	32	4491	0.03	0.01	Over	0.22	0.27	0.03	M175T546
	Arginine biosynthesis	3	34	23	4491	0.09	0.01	Over	0.00	0.01	0.13	M132T488;M175T546;M147T420
	Alanine, aspartate and glutamate metabolism	5	34	28	4491	0.15	0.01	Over	0.00	0.00	0.18	M89T21;M132T488;M147T420;M191T574;M174T394
	Glycine, serine and threonine metabolism	3	34	48	4491	0.09	0.01	Over	0.01	0.03	0.06	M132T488;M143T306;M71T50
	Cysteine and methionine metabolism	2	34	68	4491	0.06	0.02	Over	0.09	0.16	0.03	M89T21;M132T488

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Valine, leucine and isoleucine degradation	1	34	42	4491	0.03	0.01	Over	0.27	0.32	0.02	M130T268
	Valine, leucine and isoleucine biosynthesis	1	34	23	4491	0.03	0.01	Over	0.16	0.23	0.04	M130T268
	Lysine degradation	2	34	56	4491	0.06	0.01	Over	0.07	0.13	0.04	M147T590;M277T156
	Arginine and proline metabolism	5	34	71	4491	0.15	0.02	Over	0.00	0.00	0.07	M175T546;M146T276;M146T347;M131T314;M116T272
	Histidine metabolism	2	34	47	4491	0.06	0.01	Over	0.05	0.11	0.04	M132T488;M225T422
	Tryptophan metabolism	1	34	83	4491	0.03	0.02	Over	0.47	0.48	0.01	M130T71
	Phenylalanine, tyrosine and tryptophan biosynthesis	1	34	35	4491	0.03	0.01	Over	0.23	0.28	0.03	M259T250
	Caffeine metabolism	1	34	22	4491	0.03	0.00	Over	0.15	0.22	0.05	M151T209
	Neomycin, kanamycin and gentamicin biosynthesis	2	34	81	4491	0.06	0.02	Over	0.12	0.20	0.02	M179T176;M241T78
	Glycolysis / Gluconeogenesis	2	34	31	4491	0.06	0.01	Over	0.02	0.07	0.06	M179T176;M169T341
	Citrate cycle (TCA cycle)	1	34	20	4491	0.03	0.00	Over	0.14	0.21	0.05	M191T574
	Pentose phosphate pathway	2	34	37	4491	0.06	0.01	Over	0.03	0.09	0.05	M179T176;M143T306
	Pentose and glucuronate interconversions	1	34	59	4491	0.03	0.01	Over	0.36	0.39	0.02	M169T341
	Fructose and mannose metabolism	3	34	55	4491	0.09	0.01	Over	0.01	0.04	0.05	M169T341;M217T30_1;M259T250
	Galactose metabolism	3	34	46	4491	0.09	0.01	Over	0.00	0.02	0.07	M179T176;M169T341;M217T30_1
	Starch and sucrose metabolism	2	34	37	4491	0.06	0.01	Over	0.03	0.09	0.05	M179T176;M241T78
	Amino sugar and nucleotide sugar metabolism	3	34	119	4491	0.09	0.03	Over	0.06	0.13	0.03	M179T176;M217T30_1;M308T372
	Inositol phosphate metabolism	2	34	47	4491	0.06	0.01	Over	0.05	0.11	0.04	M241T78;M169T341
	Pyruvate metabolism	1	34	32	4491	0.03	0.01	Over	0.22	0.27	0.03	M71T50
	Glyoxylate and dicarboxylate metabolism	4	34	64	4491	0.12	0.01	Over	0.00	0.01	0.06	M147T420;M169T341;M191T574;M143T306
	Propanoate metabolism	2	34	41	4491	0.06	0.01	Over	0.04	0.10	0.05	M169T341;M71T50
	Butanoate metabolism	1	34	47	4491	0.03	0.01	Over	0.30	0.34	0.02	M133T33
	Nitrogen metabolism	1	26	20	4491	0.04	0.00	Over	0.11	0.18	0.05	M148T390
	Metabolic pathways	22	26	3101	4491	0.85	0.69	Over	0.06	0.13	0.01	M148T390;M111T77;M136T150;M123T59;M761T37;M268T158;M135T159;M132T337;M300T35;M112T187;M306T250;M157T284;M103T283;M407T218;M137T330;M302T57;M239T415;M241T405;M165T244;M393T34;M166T235;M227T36;M253T36_2
	Carbon metabolism	1	26	112	4491	0.04	0.02	Over	0.48	0.50	0.01	M148T390
	2-Oxocarboxylic acid metabolism	2	26	144	4491	0.08	0.03	Over	0.20	0.25	0.01	M148T390;M157T284
	Biosynthesis of amino acids	2	26	128	4491	0.08	0.03	Over	0.17	0.22	0.02	M148T390;M157T284
	Nucleotide metabolism	6	26	58	4491	0.23	0.01	Over	0.00	0.00	0.10	M111T77;M136T150;M268T158;M135T159;M112T187;M306T250
	Biosynthesis of cofactors	2	26	328	4491	0.08	0.07	Over	0.58	0.58	0.01	M148T390;M123T59
	Fatty acid biosynthesis	2	26	58	4491	0.08	0.01	Over	0.04	0.13	0.03	M227T36;M253T36_2
	Primary bile acid biosynthesis	2	26	47	4491	0.08	0.01	Over	0.03	0.13	0.04	M407T218;M393T34
	Glycerophospholipid metabolism	3	26	56	4491	0.12	0.01	Over	0.00	0.04	0.05	M761T37;M104T257_2;M524T181
	Ether lipid metabolism	1	26	25	4491	0.04	0.01	Over	0.14	0.20	0.04	M104T257_2
	Arachidonic acid metabolism	1	26	79	4491	0.04	0.02	Over	0.37	0.39	0.01	M761T37
	Linoleic acid metabolism	1	26	29	4491	0.04	0.01	Over	0.16	0.22	0.03	M761T37
	alpha-Linolenic acid metabolism	1	26	44	4491	0.04	0.01	Over	0.23	0.27	0.02	M761T37
	Sphingolipid metabolism	2	26	35	4491	0.08	0.01	Over	0.02	0.11	0.06	M300T35;M302T57
	Nicotinate and nicotinamide metabolism	1	26	55	4491	0.04	0.01	Over	0.27	0.30	0.02	M123T59
	Pantothenate and CoA biosynthesis	1	26	30	4491	0.04	0.01	Over	0.16	0.22	0.03	M111T77

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Porphyrin metabolism	1	26	148	4491	0.04	0.03	Over	0.58	0.58	0.01	M148T390
	beta-Alanine metabolism	2	26	32	4491	0.08	0.01	Over	0.01	0.10	0.06	M111T77;M239T415;M241T405
	Taurine and hypotaurine metabolism	1	26	24	4491	0.04	0.01	Over	0.13	0.20	0.04	M148T390
	D-Amino acid metabolism	1	26	69	4491	0.04	0.02	Over	0.33	0.36	0.01	M148T390
	Glutathione metabolism	1	26	38	4491	0.04	0.01	Over	0.20	0.25	0.03	M148T390
	Purine metabolism	4	26	101	4491	0.15	0.02	Over	0.00	0.03	0.04	M136T150;M268T158;M135T159;M306T250
	Pyrimidine metabolism	2	26	66	4491	0.08	0.01	Over	0.06	0.13	0.03	M111T77;M112T187
	Vascular smooth muscle contraction	1	26	16	4491	0.04	0.00	Over	0.09	0.16	0.06	M268T158
	Protein digestion and absorption	1	26	47	4491	0.04	0.01	Over	0.24	0.28	0.02	M148T390
	Bile secretion	2	26	97	4491	0.08	0.02	Over	0.11	0.18	0.02	M407T218;M393T34
	Vitamin digestion and absorption	1	26	42	4491	0.04	0.01	Over	0.22	0.26	0.02	M123T59
	Regulation of lipolysis in adipocytes	1	26	14	4491	0.04	0.00	Over	0.08	0.15	0.07	M268T158
	Renin secretion	1	26	17	4491	0.04	0.00	Over	0.09	0.17	0.06	M268T158
	Circadian entrainment	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Proximal tubule bicarbonate reclamation	1	26	17	4491	0.04	0.00	Over	0.09	0.17	0.06	M148T390
	Long-term potentiation	1	26	7	4491	0.04	0.00	Over	0.04	0.13	0.14	M148T390
	Synaptic vesicle cycle	1	26	12	4491	0.04	0.00	Over	0.07	0.13	0.08	M148T390
	Retrograde endocannabinoid signaling	2	26	19	4491	0.08	0.00	Over	0.01	0.05	0.11	M148T390;M761T37
	Glutamatergic synapse	1	26	8	4491	0.04	0.00	Over	0.05	0.13	0.13	M148T390
	GABAergic synapse	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Long-term depression	1	26	9	4491	0.04	0.00	Over	0.05	0.13	0.11	M148T390
	Taste transduction	1	26	32	4491	0.04	0.01	Over	0.17	0.22	0.03	M148T390
cluster 4	Pyruvate metabolism	3	13	32	4491	0.23	0.01	Over	0.00	0.01	0.09	M87T114;M117T93;M380T381
	Propanoate metabolism	3	13	41	4491	0.23	0.01	Over	0.00	0.01	0.07	M117T93;M117T389;M103T181
	Tyrosine metabolism	3	13	78	4491	0.23	0.02	Over	0.00	0.02	0.04	M87T114;M117T93;M200T246
	Citrate cycle (TCA cycle)	2	13	20	4491	0.15	0.00	Over	0.00	0.02	0.10	M87T114;M117T93
	Glucagon signaling pathway	2	13	26	4491	0.15	0.01	Over	0.00	0.03	0.08	M87T114;M117T93
	Alanine, aspartate and glutamate metabolism	2	13	28	4491	0.15	0.01	Over	0.00	0.03	0.07	M87T114;M117T93
	Pantothenate and CoA biosynthesis	2	13	30	4491	0.15	0.01	Over	0.00	0.03	0.07	M87T114;M202T52
	Central carbon metabolism in cancer	2	13	37	4491	0.15	0.01	Over	0.00	0.04	0.05	M87T114;M117T93
	Butanoate metabolism	2	13	47	4491	0.15	0.01	Over	0.01	0.05	0.04	M87T114;M117T93
	Phenylalanine metabolism	2	13	49	4491	0.15	0.01	Over	0.01	0.05	0.04	M87T114;M117T93
	Nicotinate and nicotinamide metabolism	2	13	55	4491	0.15	0.01	Over	0.01	0.05	0.04	M87T114;M117T93
	Lysine degradation	2	13	56	4491	0.15	0.01	Over	0.01	0.05	0.04	M117T93;M113T300
	Pentose and glucuronate interconversions	2	13	59	4491	0.15	0.01	Over	0.01	0.05	0.03	M87T114;M133T186
	Glyoxylate and dicarboxylate metabolism	2	13	64	4491	0.15	0.01	Over	0.01	0.06	0.03	M87T114;M117T93
	Type II diabetes mellitus	1	13	6	4491	0.08	0.00	Over	0.02	0.07	0.17	M87T114
	GABAergic synapse	1	13	9	4491	0.08	0.00	Over	0.03	0.09	0.11	M117T93
	Prostate cancer	1	13	11	4491	0.08	0.00	Over	0.03	0.10	0.09	M271T134
	Oxidative phosphorylation	1	13	12	4491	0.08	0.00	Over	0.03	0.10	0.08	M117T93
	Insulin secretion	1	13	12	4491	0.08	0.00	Over	0.03	0.10	0.08	M87T114
	Dopaminergic synapse	1	13	12	4491	0.08	0.00	Over	0.03	0.10	0.08	M200T246
	Carbon metabolism	2	13	112	4491	0.15	0.02	Over	0.04	0.11	0.02	M87T114;M117T93

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	HIF-1 signaling pathway	1	13	15	4491	0.08	0.00	Over	0.04	0.11	0.07	M87T114
	Insulin resistance	1	13	19	4491	0.08	0.00	Over	0.05	0.13	0.05	M87T114
	Metabolic pathways	12	13	3101	4491	0.92	0.69	Over	0.06	0.13	0.00	M87T114;M117T93;M365T379;M133T186;M113T300;M202T52;M271T134;M117T389;M243T217;M380T381;M200T246;M181T61
	AMPK signaling pathway	1	13	22	4491	0.08	0.00	Over	0.06	0.13	0.05	M87T114
	Caffeine metabolism	1	13	22	4491	0.08	0.00	Over	0.06	0.13	0.05	M181T61
	Valine, leucine and isoleucine biosynthesis	1	13	23	4491	0.08	0.01	Over	0.06	0.13	0.04	M87T114
	Riboflavin metabolism	1	13	24	4491	0.08	0.01	Over	0.07	0.13	0.04	M133T186
	Taurine and hypotaurine metabolism	1	13	24	4491	0.08	0.01	Over	0.07	0.13	0.04	M87T114
	Ovarian steroidogenesis	1	13	24	4491	0.08	0.01	Over	0.07	0.13	0.04	M271T134
	cAMP signaling pathway	1	13	25	4491	0.08	0.01	Over	0.07	0.13	0.04	M117T93
	Pathways in cancer	1	13	31	4491	0.08	0.01	Over	0.09	0.15	0.03	M271T134
	Glycolysis / Gluconeogenesis	1	13	31	4491	0.08	0.01	Over	0.09	0.15	0.03	M87T114
	Thiamine metabolism	1	13	31	4491	0.08	0.01	Over	0.09	0.15	0.03	M87T114
	beta-Alanine metabolism	1	13	32	4491	0.08	0.01	Over	0.09	0.15	0.03	M202T52
	Sulfur metabolism	1	13	34	4491	0.08	0.01	Over	0.09	0.15	0.03	M117T93
	Pentose phosphate pathway	1	13	37	4491	0.08	0.01	Over	0.10	0.16	0.03	M87T114
	Starch and sucrose metabolism	1	13	37	4491	0.08	0.01	Over	0.10	0.16	0.03	M365T379
	Diabetic cardiomyopathy	1	13	39	4491	0.08	0.01	Over	0.11	0.16	0.03	M87T114
	Valine, leucine and isoleucine degradation	1	13	42	4491	0.08	0.01	Over	0.12	0.16	0.02	M117T389
	Vitamin digestion and absorption	1	13	42	4491	0.08	0.01	Over	0.12	0.16	0.02	M202T52
	Lipoic acid metabolism	1	13	44	4491	0.08	0.01	Over	0.12	0.17	0.02	M87T114
	Terpenoid backbone biosynthesis	1	13	46	4491	0.08	0.01	Over	0.13	0.17	0.02	M87T114
	Glycine, serine and threonine metabolism	1	13	48	4491	0.08	0.01	Over	0.13	0.17	0.02	M87T114
	Fatty acid degradation	1	13	50	4491	0.08	0.01	Over	0.14	0.17	0.02	M113T300
	Fructose and mannose metabolism	1	13	55	4491	0.08	0.01	Over	0.15	0.19	0.02	M243T217
	Phosphonate and phosphinate metabolism	1	13	56	4491	0.08	0.01	Over	0.15	0.19	0.02	M87T114
	Ascorbate and aldarate metabolism	1	13	57	4491	0.08	0.01	Over	0.15	0.19	0.02	M87T114
	Pyrimidine metabolism	1	13	66	4491	0.08	0.01	Over	0.18	0.21	0.02	M117T389
	Cysteine and methionine metabolism	1	13	68	4491	0.08	0.02	Over	0.18	0.21	0.01	M87T114
	D-Amino acid metabolism	1	13	69	4491	0.08	0.02	Over	0.18	0.21	0.01	M87T114
	Arginine and proline metabolism	1	13	71	4491	0.08	0.02	Over	0.19	0.21	0.01	M87T114
	Biosynthesis of cofactors	2	13	328	4491	0.15	0.07	Over	0.24	0.27	0.01	M87T114;M202T52
	Steroid hormone biosynthesis	1	13	101	4491	0.08	0.02	Over	0.26	0.28	0.01	M271T134
	Amino sugar and nucleotide sugar metabolism	1	13	119	4491	0.08	0.03	Over	0.30	0.31	0.01	M243T217
	Biosynthesis of amino acids	1	13	128	4491	0.08	0.03	Over	0.31	0.32	0.01	M87T114
	2-Oxocarboxylic acid metabolism	1	13	144	4491	0.08	0.03	Over	0.35	0.35	0.01	M87T114
	Biosynthesis of nucleotide sugars	1	13	200	4491	0.08	0.04	Over	0.45	0.45	0.01	M243T217
cluster 5	Efferocytosis	1	15	21	4491	0.07	0.00	Over	0.07	0.19	0.05	M399T133
	ABC transporters	5	15	138	4491	0.33	0.03	Over	0.00	0.00	0.04	M166T263;M171T384;M116T308;M341T388;M377T387;M124T292

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Neuroactive ligand-receptor interaction	1	15	53	4491	0.07	0.01	Over	0.16	0.22	0.02	M124T292
	Sulfur relay system	1	15	11	4491	0.07	0.00	Over	0.04	0.13	0.09	M399T133
	Aminoacyl-tRNA biosynthesis	2	15	52	4491	0.13	0.01	Over	0.01	0.06	0.04	M166T263;M116T308
	Chemical carcinogenesis - reactive oxygen species	1	15	57	4491	0.07	0.01	Over	0.17	0.22	0.02	M399T133
	Central carbon metabolism in cancer	2	15	37	4491	0.13	0.01	Over	0.01	0.04	0.05	M166T263;M116T308
	Choline metabolism in cancer	1	15	11	4491	0.07	0.00	Over	0.04	0.13	0.09	M171T384
	Arginine biosynthesis	1	15	23	4491	0.07	0.01	Over	0.07	0.19	0.04	M188T390
	Cysteine and methionine metabolism	1	15	68	4491	0.07	0.02	Over	0.20	0.23	0.01	M399T133
	Arginine and proline metabolism	3	15	71	4491	0.20	0.02	Over	0.00	0.01	0.04	M399T133;M116T308;M114T47
	Tyrosine metabolism	1	15	78	4491	0.07	0.02	Over	0.23	0.26	0.01	M181T344
	Phenylalanine metabolism	1	15	49	4491	0.07	0.01	Over	0.15	0.22	0.02	M166T263
	Phenylalanine, tyrosine and tryptophan biosynthesis	1	15	35	4491	0.07	0.01	Over	0.11	0.19	0.03	M166T263
	Ascorbate and aldarate metabolism	1	15	57	4491	0.07	0.01	Over	0.17	0.22	0.02	M177T156
	Starch and sucrose metabolism	1	15	37	4491	0.07	0.01	Over	0.12	0.19	0.03	M341T388;M377T387
	Sulfur metabolism	1	15	34	4491	0.07	0.01	Over	0.11	0.19	0.03	M124T292
	Metabolic pathways	14	15	3101	4491	0.93	0.69	Over	0.03	0.13	0.00	M399T133;M455T30;M166T263;M171T384;M116T308;M341T388;M377T387;M124T292;M103T401;M188T390;M114T47;M117T444;M177T156;M367T29;M181T344
	2-Oxocarboxylic acid metabolism	2	15	144	4491	0.13	0.03	Over	0.08	0.19	0.01	M166T263;M188T390
	Fatty acid metabolism	1	15	122	4491	0.07	0.03	Over	0.34	0.34	0.01	M103T401
	Biosynthesis of amino acids	4	15	128	4491	0.27	0.03	Over	0.00	0.01	0.03	M399T133;M166T263;M116T308;M188T390
	Biosynthesis of cofactors	2	15	328	4491	0.13	0.07	Over	0.30	0.31	0.01	M399T133;M455T30
	Fatty acid biosynthesis	1	15	58	4491	0.07	0.01	Over	0.18	0.22	0.02	M103T401
	Primary bile acid biosynthesis	1	15	47	4491	0.07	0.01	Over	0.15	0.22	0.02	M124T292
	Steroid hormone biosynthesis	1	15	101	4491	0.07	0.02	Over	0.29	0.31	0.01	M367T29
	Glycerolipid metabolism	1	15	38	4491	0.07	0.01	Over	0.12	0.19	0.03	M171T384
	Glycerophospholipid metabolism	1	15	56	4491	0.07	0.01	Over	0.17	0.22	0.02	M171T384
	Riboflavin metabolism	1	15	24	4491	0.07	0.01	Over	0.08	0.19	0.04	M455T30
	Pantothenate and CoA biosynthesis	1	15	30	4491	0.07	0.01	Over	0.10	0.19	0.03	M204T65
	beta-Alanine metabolism	1	15	32	4491	0.07	0.01	Over	0.10	0.19	0.03	M103T401
	Taurine and hypotaurine metabolism	1	15	24	4491	0.07	0.01	Over	0.08	0.19	0.04	M124T292
	D-Amino acid metabolism	3	15	69	4491	0.20	0.02	Over	0.00	0.01	0.04	M166T263;M116T308;M188T390
	Pyrimidine metabolism	1	15	66	4491	0.07	0.01	Over	0.20	0.23	0.02	M103T401
	Carbohydrate digestion and absorption	1	15	27	4491	0.07	0.01	Over	0.09	0.19	0.04	M341T388;M377T387
	Protein digestion and absorption	2	15	47	4491	0.13	0.01	Over	0.01	0.06	0.04	M166T263;M116T308
	Bile secretion	1	15	97	4491	0.07	0.02	Over	0.28	0.30	0.01	M367T29
	Vitamin digestion and absorption	1	15	42	4491	0.07	0.01	Over	0.13	0.21	0.02	M455T30
	Mineral absorption	2	15	29	4491	0.13	0.01	Over	0.00	0.03	0.07	M166T263;M116T308
	Taste transduction	1	15	32	4491	0.07	0.01	Over	0.10	0.19	0.03	M341T388;M377T387
cluster 6	Biosynthesis of unsaturated fatty acids	6	16	74	4491	0.38	0.02	Over	0.00	0.00	0.08	

Clusters	Pathway Name	Test	TestAll	Ref	Ref All	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich Factor	Metabolite Name
	Biotin metabolism	2	16	29	4491	0.13	0.01	Over	0.00	0.06	0.07	
	ABC transporters	3	16	138	4491	0.19	0.03	Over	0.01	0.10	0.02	
	Fatty acid biosynthesis	2	16	58	4491	0.13	0.01	Over	0.02	0.10	0.03	
	Epithelial cell signaling in Helicobacter pylori infection	1	16	5	4491	0.06	0.00	Over	0.02	0.10	0.20	
	Pyrimidine metabolism	2	16	66	4491	0.13	0.01	Over	0.02	0.10	0.03	
	Arachidonic acid metabolism	2	16	79	4491	0.13	0.02	Over	0.03	0.13	0.03	
	Choline metabolism in cancer	1	16	11	4491	0.06	0.00	Over	0.04	0.13	0.09	
	Arginine biosynthesis	1	16	23	4491	0.06	0.01	Over	0.08	0.25	0.04	
	Linoleic acid metabolism	1	16	29	4491	0.06	0.01	Over	0.10	0.26	0.03	
	Glutathione metabolism	1	16	38	4491	0.06	0.01	Over	0.13	0.26	0.03	
	Fatty acid elongation	1	16	40	4491	0.06	0.01	Over	0.13	0.26	0.03	
	Histidine metabolism	1	16	47	4491	0.06	0.01	Over	0.16	0.26	0.02	
	Protein digestion and absorption	1	16	47	4491	0.06	0.01	Over	0.16	0.26	0.02	
	Fatty acid degradation	1	16	50	4491	0.06	0.01	Over	0.16	0.26	0.02	
	Aminoacyl-tRNA biosynthesis	1	16	52	4491	0.06	0.01	Over	0.17	0.26	0.02	
	Lysine degradation	1	16	56	4491	0.06	0.01	Over	0.18	0.26	0.02	
	Glycerophospholipid metabolism	1	16	56	4491	0.06	0.01	Over	0.18	0.26	0.02	
	Steroid biosynthesis	1	16	57	4491	0.06	0.01	Over	0.19	0.26	0.02	
	Nucleotide metabolism	1	16	58	4491	0.06	0.01	Over	0.19	0.26	0.02	
	D-Amino acid metabolism	1	16	69	4491	0.06	0.02	Over	0.22	0.29	0.01	
	Arginine and proline metabolism	1	16	71	4491	0.06	0.02	Over	0.23	0.29	0.01	
	Steroid hormone biosynthesis	1	16	101	4491	0.06	0.02	Over	0.31	0.36	0.01	
	Purine metabolism	1	16	101	4491	0.06	0.02	Over	0.31	0.36	0.01	
	Fatty acid metabolism	1	16	122	4491	0.06	0.03	Over	0.36	0.40	0.01	
	Biosynthesis of amino acids	1	16	128	4491	0.06	0.03	Over	0.37	0.40	0.01	
	2-Oxocarboxylic acid metabolism	1	16	144	4491	0.06	0.03	Over	0.41	0.42	0.01	
	Metabolic pathways	12	16	3101	4491	0.75	0.69	Over	0.42	0.42	0.00	

Table S3. KEGG enrichment of upper airway metabolite clusters.

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
cluster 1	ABC transporters	2	10	138	4491	0.2	0.03	Over	0.04	0.08	0.01	M365T416;M569T449
	cGMP-PKG signaling pathway	1	10	10	4491	0.1	0.00	Over	0.02	0.08	0.10	M348T452
	cAMP signaling pathway	1	10	25	4491	0.1	0.01	Over	0.05	0.09	0.04	M348T452
	FoxO signaling pathway	1	10	5	4491	0.1	0.00	Over	0.01	0.08	0.20	M348T452
	mTOR signaling pathway	1	10	4	4491	0.1	0.00	Over	0.01	0.08	0.25	M348T452
	PI3K-Akt signaling pathway	1	10	4	4491	0.1	0.00	Over	0.01	0.08	0.25	M348T452
	AMPK signaling pathway	1	10	22	4491	0.1	0.00	Over	0.05	0.09	0.05	M348T452
	Antifolate resistance	1	10	17	4491	0.1	0.00	Over	0.04	0.08	0.06	M348T452
	Cushing syndrome	1	10	13	4491	0.1	0.00	Over	0.03	0.08	0.08	M348T452
	Parkinson disease	1	10	26	4491	0.1	0.01	Over	0.06	0.09	0.04	M348T452
	Pathways of neurodegeneration - multiple diseases	1	10	32	4491	0.1	0.01	Over	0.07	0.10	0.03	M348T452
	Morphine addiction	1	10	8	4491	0.1	0.00	Over	0.02	0.08	0.13	M348T452
	Arginine biosynthesis	1	10	23	4491	0.1	0.01	Over	0.05	0.09	0.04	M198T386
	Tyrosine metabolism	1	10	78	4491	0.1	0.02	Over	0.16	0.19	0.01	M200T246
	Tryptophan metabolism	1	10	83	4491	0.1	0.02	Over	0.17	0.19	0.01	M136T50
	Caffeine metabolism	1	10	22	4491	0.1	0.00	Over	0.05	0.09	0.05	M569T449
	Fructose and mannose metabolism	1	10	55	4491	0.1	0.01	Over	0.12	0.16	0.02	M243T217
	Galactose metabolism	1	10	46	4491	0.1	0.01	Over	0.10	0.14	0.02	M365T416
	Amino sugar and nucleotide sugar metabolism	1	10	119	4491	0.1	0.03	Over	0.24	0.25	0.01	M243T217
	Metabolic pathways	9	10	3101	4491	0.9	0.69	Over	0.13	0.17	0.00	M348T452;M365T416;M198T386;M136T50; M569T449;M243T217;M200T246;M227T36; M465T26
	Biosynthesis of amino acids	1	10	128	4491	0.1	0.03	Over	0.25	0.26	0.01	M198T386
	Nucleotide metabolism	2	10	58	4491	0.2	0.01	Over	0.01	0.08	0.03	M348T452;M569T449
	Biosynthesis of cofactors	2	10	328	4491	0.2	0.07	Over	0.16	0.19	0.01	M348T452;M136T50
	Biosynthesis of nucleotide sugars	1	10	200	4491	0.1	0.04	Over	0.37	0.37	0.01	M243T217
	Fatty acid biosynthesis	1	10	58	4491	0.1	0.01	Over	0.12	0.16	0.02	M227T36
	Steroid hormone biosynthesis	1	10	101	4491	0.1	0.02	Over	0.20	0.22	0.01	M465T26
	Biosynthesis of unsaturated fatty acids	1	10	74	4491	0.1	0.02	Over	0.15	0.19	0.01	M321T34
	Purine metabolism	2	10	101	4491	0.2	0.02	Over	0.02	0.08	0.02	M348T452;M569T449
	Longevity regulating pathway	1	10	8	4491	0.1	0.00	Over	0.02	0.08	0.13	M348T452
	Carbohydrate digestion and absorption	1	10	27	4491	0.1	0.01	Over	0.06	0.09	0.04	M365T416
	Regulation of lipolysis in adipocytes	1	10	14	4491	0.1	0.00	Over	0.03	0.08	0.07	M348T452
	Renin secretion	1	10	17	4491	0.1	0.00	Over	0.04	0.08	0.06	M348T452
	Aldosterone synthesis and secretion	1	10	22	4491	0.1	0.00	Over	0.05	0.09	0.05	M348T452
	Cortisol synthesis and secretion	1	10	12	4491	0.1	0.00	Over	0.03	0.08	0.08	M348T452
	Parathyroid hormone synthesis, secretion and action	1	10	11	4491	0.1	0.00	Over	0.02	0.08	0.09	M348T452
	Dopaminergic synapse	1	10	12	4491	0.1	0.00	Over	0.03	0.08	0.08	M200T246
	Olfactory transduction	1	10	8	4491	0.1	0.00	Over	0.02	0.08	0.13	M348T452
	Taste transduction	1	10	32	4491	0.1	0.01	Over	0.07	0.10	0.03	M348T452
cluster 2	cAMP signaling pathway	1	17	25	4491	0.06	0.01	Over	0.09	0.19	0.04	M87T361

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Neuroactive ligand-receptor interaction	1	17	53	4491	0.06	0.01	Over	0.18	0.24	0.02	M606T494
	Choline metabolism in cancer	2	17	11	4491	0.12	0.00	Over	0.00	0.02	0.18	M761T37;M184T510
	Autoimmune thyroid disease	1	17	3	4491	0.06	0.00	Over	0.01	0.10	0.33	M606T494
	Alanine, aspartate and glutamate metabolism	1	17	28	4491	0.06	0.01	Over	0.10	0.19	0.04	M464T335_2
	Cysteine and methionine metabolism	1	17	68	4491	0.06	0.02	Over	0.23	0.27	0.01	M298T93
	Histidine metabolism	2	17	47	4491	0.12	0.01	Over	0.01	0.10	0.04	M137T330;M239T415;M241T405
	Tyrosine metabolism	1	17	78	4491	0.06	0.02	Over	0.26	0.28	0.01	M606T494
	Pentose and glucuronate interconversions	1	17	59	4491	0.06	0.01	Over	0.20	0.25	0.02	M133T186
	Pyruvate metabolism	1	17	32	4491	0.06	0.01	Over	0.11	0.19	0.03	M380T381
	Butanoate metabolism	1	17	47	4491	0.06	0.01	Over	0.16	0.24	0.02	M87T361
	Metabolic pathways	14	17	3101	4491	0.82	0.69	Over	0.18	0.24	0.00	M761T37;M298T93;M135T159;M133T186;M184T510;M137T330;M87T361;M239T415;M241T405;M606T494;M393T34;M380T381;M474T246;M464T335_2;M253T36_2
	Fatty acid metabolism	1	17	122	4491	0.06	0.03	Over	0.37	0.39	0.01	M400T147
	Nucleotide metabolism	2	17	58	4491	0.12	0.01	Over	0.02	0.10	0.03	M135T159;M464T335_2
	Biosynthesis of cofactors	1	17	328	4491	0.06	0.07	Under	0.73	0.73	0.00	M464T335_2
	Fatty acid biosynthesis	1	17	58	4491	0.06	0.01	Over	0.20	0.25	0.02	M253T36_2
	Fatty acid degradation	1	17	50	4491	0.06	0.01	Over	0.17	0.24	0.02	M400T147
	Primary bile acid biosynthesis	2	17	47	4491	0.12	0.01	Over	0.01	0.10	0.04	M393T34;M401T34
	Glycerophospholipid metabolism	2	17	56	4491	0.12	0.01	Over	0.02	0.10	0.04	M761T37;M184T510
	Arachidonic acid metabolism	1	17	79	4491	0.06	0.02	Over	0.26	0.28	0.01	M761T37
	Linoleic acid metabolism	1	17	29	4491	0.06	0.01	Over	0.10	0.19	0.03	M761T37
	alpha-Linolenic acid metabolism	1	17	44	4491	0.06	0.01	Over	0.15	0.24	0.02	M761T37
	Biosynthesis of unsaturated fatty acids	1	17	74	4491	0.06	0.02	Over	0.25	0.28	0.01	M309T37
	One carbon pool by folate	1	17	9	4491	0.06	0.00	Over	0.03	0.15	0.11	M474T246
	Riboflavin metabolism	1	17	24	4491	0.06	0.01	Over	0.09	0.19	0.04	M133T186
	beta-Alanine metabolism	1	17	32	4491	0.06	0.01	Over	0.11	0.19	0.03	M239T415;M241T405
	Purine metabolism	2	17	101	4491	0.12	0.02	Over	0.05	0.18	0.02	M135T159;M464T335_2
	Bile secretion	2	17	97	4491	0.12	0.02	Over	0.05	0.18	0.02	M606T494;M393T34
	Thyroid hormone synthesis	1	17	21	4491	0.06	0.00	Over	0.08	0.19	0.05	M606T494
	Thyroid hormone signaling pathway	1	17	11	4491	0.06	0.00	Over	0.04	0.16	0.09	M606T494
	Thermogenesis	1	17	23	4491	0.06	0.01	Over	0.08	0.19	0.04	M606T494
	Retrograde endocannabinoid signaling	1	17	19	4491	0.06	0.00	Over	0.07	0.19	0.05	M761T37
cluster 3	Lysosome	1	30	4	4491	0.03	0.00	Over	0.03	0.12	0.25	M217T30_1
	ABC transporters	4	30	138	4491	0.13	0.03	Over	0.01	0.09	0.03	M61T94;M116T308;M217T30_1;M243T148
	cAMP signaling pathway	1	30	25	4491	0.03	0.01	Over	0.15	0.27	0.04	M103T233
	HIF-1 signaling pathway	1	30	15	4491	0.03	0.00	Over	0.10	0.21	0.07	M87T114
	AMPK signaling pathway	1	30	22	4491	0.03	0.00	Over	0.14	0.27	0.05	M87T114
	Aminoacyl-tRNA biosynthesis	1	30	52	4491	0.03	0.01	Over	0.30	0.35	0.02	M116T308
	Chemical carcinogenesis - reactive oxygen species	1	30	57	4491	0.03	0.01	Over	0.32	0.36	0.02	M289T40_1
	Central carbon metabolism in cancer	4	30	37	4491	0.13	0.01	Over	0.00	0.01	0.11	M87T114;M241T78;M116T308;M191T574
	Diabetic cardiomyopathy	2	30	39	4491	0.07	0.01	Over	0.03	0.12	0.05	M87T114;M241T78
	Type II diabetes mellitus	1	30	6	4491	0.03	0.00	Over	0.04	0.15	0.17	M87T114

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Insulin resistance	2	30	19	4491	0.07	0.00	Over	0.01	0.09	0.11	M87T114;M241T78
	Epithelial cell signaling in Helicobacter pylori infection	1	30	5	4491	0.03	0.00	Over	0.03	0.14	0.20	M61T94
	Arginine biosynthesis	2	30	23	4491	0.07	0.01	Over	0.01	0.09	0.09	M61T94;M157T284
	Alanine, aspartate and glutamate metabolism	2	30	28	4491	0.07	0.01	Over	0.01	0.09	0.07	M87T114;M191T574
	Glycine, serine and threonine metabolism	2	30	48	4491	0.07	0.01	Over	0.04	0.15	0.04	M87T114;M103T283
	Cysteine and methionine metabolism	1	30	68	4491	0.03	0.02	Over	0.37	0.40	0.01	M87T114
	Valine, leucine and isoleucine degradation	1	30	42	4491	0.03	0.01	Over	0.25	0.33	0.02	M117T389
	Valine, leucine and isoleucine biosynthesis	1	30	23	4491	0.03	0.01	Over	0.14	0.27	0.04	M87T114
	Lysine degradation	2	30	56	4491	0.07	0.01	Over	0.05	0.16	0.04	M147T590;M113T300
	Arginine and proline metabolism	4	30	71	4491	0.13	0.02	Over	0.00	0.04	0.06	M87T114;M61T94;M116T308;M146T367
	Histidine metabolism	1	30	47	4491	0.03	0.01	Over	0.27	0.33	0.02	M137T289
	Tyrosine metabolism	2	30	78	4491	0.07	0.02	Over	0.09	0.21	0.03	M87T114;M181T344
	Phenylalanine metabolism	2	30	49	4491	0.07	0.01	Over	0.04	0.15	0.04	M87T114;M166T235
	Caffeine metabolism	1	30	22	4491	0.03	0.00	Over	0.14	0.27	0.05	M181T61
	Neomycin, kanamycin and gentamicin biosynthesis	1	30	81	4491	0.03	0.02	Over	0.42	0.44	0.01	M241T78
	Glycolysis / Gluconeogenesis	1	30	31	4491	0.03	0.01	Over	0.19	0.29	0.03	M87T114
	Citrate cycle (TCA cycle)	2	30	20	4491	0.07	0.00	Over	0.01	0.09	0.10	M87T114;M191T574
	Pentose phosphate pathway	1	30	37	4491	0.03	0.01	Over	0.22	0.32	0.03	M87T114
	Pentose and glucuronate interconversions	1	30	59	4491	0.03	0.01	Over	0.33	0.36	0.02	M87T114
	Fructose and mannose metabolism	1	30	55	4491	0.03	0.01	Over	0.31	0.36	0.02	M217T30_1
	Galactose metabolism	1	30	46	4491	0.03	0.01	Over	0.27	0.33	0.02	M217T30_1
	Ascorbate and aldarate metabolism	1	30	57	4491	0.03	0.01	Over	0.32	0.36	0.02	M87T114
	Starch and sucrose metabolism	2	30	37	4491	0.07	0.01	Over	0.02	0.12	0.05	M241T78;M365T379
	Amino sugar and nucleotide sugar metabolism	1	30	119	4491	0.03	0.03	Over	0.55	0.57	0.01	M217T30_1
	Inositol phosphate metabolism	1	30	47	4491	0.03	0.01	Over	0.27	0.33	0.02	M241T78
	Pyruvate metabolism	1	30	32	4491	0.03	0.01	Over	0.19	0.29	0.03	M87T114
	Glyoxylate and dicarboxylate metabolism	2	30	64	4491	0.07	0.01	Over	0.07	0.18	0.03	M87T114;M191T574
	Propanoate metabolism	1	30	41	4491	0.03	0.01	Over	0.24	0.33	0.02	M117T389
	Butanoate metabolism	2	30	47	4491	0.07	0.01	Over	0.04	0.15	0.04	M87T114;M103T233
	Metabolic pathways	26	30	3101	4491	0.87	0.69	Over	0.02	0.12	0.01	M87T114;M61T94;M241T78;M136T150;M116T308;M123T59;M191T574;M217T30_1;M255T36;M365T379;M243T148;M147T590;M157T284;M113T300;M103T283;M137T289;M146T367;M103T233;M283T34;M128T302;M117T389;M166T235;M367T29;M569T107;M181T344;M181T61
	Carbon metabolism	2	30	112	4491	0.07	0.02	Over	0.17	0.28	0.02	M87T114;M191T574
	2-Oxocarboxylic acid metabolism	3	30	144	4491	0.10	0.03	Over	0.07	0.18	0.02	M87T114;M191T574;M157T284
	Fatty acid metabolism	1	30	122	4491	0.03	0.03	Over	0.56	0.57	0.01	M255T36
	Biosynthesis of amino acids	4	30	128	4491	0.13	0.03	Over	0.01	0.09	0.03	M87T114;M116T308;M191T574;M157T284
	Nucleotide metabolism	2	30	58	4491	0.07	0.01	Over	0.06	0.16	0.03	M136T150;M243T148
	Biosynthesis of cofactors	3	30	328	4491	0.10	0.07	Over	0.38	0.40	0.01	M87T114;M123T59;M191T574
	Biosynthesis of nucleotide sugars	1	30	200	4491	0.03	0.04	Under	0.75	0.75	0.01	M217T30_1

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Fatty acid biosynthesis	2	30	58	4491	0.07	0.01	Over	0.06	0.16	0.03	M255T36;M283T34
	Fatty acid elongation	1	30	40	4491	0.03	0.01	Over	0.24	0.33	0.03	M255T36
	Fatty acid degradation	2	30	50	4491	0.07	0.01	Over	0.04	0.15	0.04	M255T36;M113T300
	Steroid hormone biosynthesis	2	30	101	4491	0.07	0.02	Over	0.15	0.27	0.02	M367T29;M289T40_1
	Arachidonic acid metabolism	2	30	79	4491	0.07	0.02	Over	0.10	0.21	0.03	M569T107;M349T77
	Biosynthesis of unsaturated fatty acids	3	30	74	4491	0.10	0.02	Over	0.01	0.09	0.04	M255T36;M283T34;M311T33
	Thiamine metabolism	1	30	31	4491	0.03	0.01	Over	0.19	0.29	0.03	M87T114
	Nicotinate and nicotinamide metabolism	2	30	55	4491	0.07	0.01	Over	0.05	0.16	0.04	M87T114;M123T59
	Pantothenate and CoA biosynthesis	2	30	30	4491	0.07	0.01	Over	0.02	0.10	0.07	M87T114;M204T65
	Biotin metabolism	1	30	29	4491	0.03	0.01	Over	0.18	0.28	0.03	M61T94
	Lipoic acid metabolism	1	30	44	4491	0.03	0.01	Over	0.26	0.33	0.02	M87T114
	Taurine and hypotaurine metabolism	1	30	24	4491	0.03	0.01	Over	0.15	0.27	0.04	M87T114
	Phosphonate and phosphinate metabolism	1	30	56	4491	0.03	0.01	Over	0.31	0.36	0.02	M87T114
	D-Amino acid metabolism	2	30	69	4491	0.07	0.02	Over	0.08	0.18	0.03	M87T114;M116T308
	Glutathione metabolism	1	30	38	4491	0.03	0.01	Over	0.23	0.32	0.03	M128T302
	Terpenoid backbone biosynthesis	1	30	46	4491	0.03	0.01	Over	0.27	0.33	0.02	M87T114
	Purine metabolism	2	30	101	4491	0.07	0.02	Over	0.15	0.27	0.02	M61T94;M136T150
	Pyrimidine metabolism	3	30	66	4491	0.10	0.01	Over	0.01	0.09	0.05	M61T94;M243T148;M117T389
	Carbohydrate digestion and absorption	1	30	27	4491	0.03	0.01	Over	0.17	0.28	0.04	M241T78
	Protein digestion and absorption	1	30	47	4491	0.03	0.01	Over	0.27	0.33	0.02	M116T308
	Bile secretion	1	30	97	4491	0.03	0.02	Over	0.48	0.50	0.01	M367T29
	Vitamin digestion and absorption	1	30	42	4491	0.03	0.01	Over	0.25	0.33	0.02	M123T59
	Mineral absorption	1	30	29	4491	0.03	0.01	Over	0.18	0.28	0.03	M116T308
	Insulin secretion	2	30	12	4491	0.07	0.00	Over	0.00	0.07	0.17	M87T114;M241T78
	Ovarian steroidogenesis	1	30	24	4491	0.03	0.01	Over	0.15	0.27	0.04	M289T40_1
	Prolactin signaling pathway	1	30	11	4491	0.03	0.00	Over	0.07	0.18	0.09	M241T78
	Thyroid hormone synthesis	1	30	21	4491	0.03	0.00	Over	0.13	0.27	0.05	M241T78
	Glucagon signaling pathway	2	30	26	4491	0.07	0.01	Over	0.01	0.09	0.08	M87T114;M191T574
	C-type lectin receptor signaling pathway	1	30	11	4491	0.03	0.00	Over	0.07	0.18	0.09	M217T30_1
	Taste transduction	1	30	32	4491	0.03	0.01	Over	0.19	0.29	0.03	M191T574
cluster 4	Ferroptosis	2	38	29	4491	0.05	0.01	Over	0.02	0.07	0.07	M148T390;M295T252
	Gap junction	1	38	11	4491	0.03	0.00	Over	0.09	0.14	0.09	M148T390
	Efferocytosis	3	38	21	4491	0.08	0.00	Over	0.00	0.00	0.14	M399T133;M179T176;M175T546
	ABC transporters	13	38	138	4491	0.34	0.03	Over	0.00	0.00	0.09	M148T390;M179T176;M89T21;M130T80;M132T488;M175T546;M147T420;M171T384;M130T268;M341T388;M377T387;M124T292;M267T210;M146T276
	HIF-1 signaling pathway	1	38	15	4491	0.03	0.00	Over	0.12	0.17	0.07	M179T176
	FoxO signaling pathway	2	38	5	4491	0.05	0.00	Over	0.00	0.00	0.40	M148T390;M179T176
	Phospholipase D signaling pathway	1	38	11	4491	0.03	0.00	Over	0.09	0.14	0.09	M148T390
	mTOR signaling pathway	2	38	4	4491	0.05	0.00	Over	0.00	0.00	0.50	M175T546;M130T268
	AMPK signaling pathway	1	38	22	4491	0.03	0.00	Over	0.17	0.23	0.05	M179T176
	Neuroactive ligand-receptor interaction	3	38	53	4491	0.08	0.01	Over	0.01	0.04	0.06	M148T390;M132T488;M124T292

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Sulfur relay system	2	38	11	4491	0.05	0.00	Over	0.00	0.02	0.18	M399T133;M89T21
	Aminoacyl-tRNA biosynthesis	7	38	52	4491	0.18	0.01	Over	0.00	0.00	0.13	M148T390;M89T21;M130T80;M132T488;M175T546;M147T420;M130T268
	Chemical carcinogenesis - reactive oxygen species	1	38	57	4491	0.03	0.01	Over	0.39	0.41	0.02	M399T133
	Central carbon metabolism in cancer	7	38	37	4491	0.18	0.01	Over	0.00	0.00	0.19	M148T390;M179T176;M89T21;M132T488;M175T546;M147T420;M130T268
	Choline metabolism in cancer	2	38	11	4491	0.05	0.00	Over	0.00	0.02	0.18	M171T384;M793T136
	Diabetic cardiomyopathy	2	38	39	4491	0.05	0.01	Over	0.04	0.10	0.05	M179T176;M71T50
	Type II diabetes mellitus	1	38	6	4491	0.03	0.00	Over	0.05	0.11	0.17	M179T176
	Insulin resistance	1	38	19	4491	0.03	0.00	Over	0.15	0.20	0.05	M179T176
	Non-alcoholic fatty liver disease	1	38	2	4491	0.03	0.00	Over	0.02	0.05	0.50	M179T176
	AGE-RAGE signaling pathway in diabetic complications	1	38	9	4491	0.03	0.00	Over	0.07	0.13	0.11	M179T176
	Shigellosis	1	38	14	4491	0.03	0.00	Over	0.11	0.16	0.07	M130T268
	Chagas disease	1	38	6	4491	0.03	0.00	Over	0.05	0.11	0.17	M175T546
	Amoebiasis	1	38	13	4491	0.03	0.00	Over	0.10	0.15	0.08	M175T546
	Amyotrophic lateral sclerosis	2	38	14	4491	0.05	0.00	Over	0.01	0.03	0.14	M148T390;M175T546
	Huntington disease	1	38	6	4491	0.03	0.00	Over	0.05	0.11	0.17	M148T390
	Spinocerebellar ataxia	1	38	7	4491	0.03	0.00	Over	0.06	0.11	0.14	M148T390
	Pathways of neurodegeneration - multiple diseases	2	38	32	4491	0.05	0.01	Over	0.03	0.08	0.06	M148T390;M175T546
	Cocaine addiction	1	38	7	4491	0.03	0.00	Over	0.06	0.11	0.14	M148T390
	Amphetamine addiction	1	38	9	4491	0.03	0.00	Over	0.07	0.13	0.11	M148T390
	Nicotine addiction	1	38	7	4491	0.03	0.00	Over	0.06	0.11	0.14	M148T390
	Alcoholism	1	38	10	4491	0.03	0.00	Over	0.08	0.13	0.10	M148T390
	Arginine biosynthesis	5	38	23	4491	0.13	0.01	Over	0.00	0.00	0.22	M148T390;M132T488;M175T546;M147T420;M188T390
	Alanine, aspartate and glutamate metabolism	5	38	28	4491	0.13	0.01	Over	0.00	0.00	0.18	M148T390;M89T21;M132T488;M147T420;M174T394
	Glycine, serine and threonine metabolism	2	38	48	4491	0.05	0.01	Over	0.06	0.11	0.04	M132T488;M71T50
	Cysteine and methionine metabolism	3	38	68	4491	0.08	0.02	Over	0.02	0.06	0.04	M399T133;M89T21;M132T488
	Valine, leucine and isoleucine degradation	1	38	42	4491	0.03	0.01	Over	0.30	0.34	0.02	M130T268
	Valine, leucine and isoleucine biosynthesis	1	38	23	4491	0.03	0.01	Over	0.18	0.23	0.04	M130T268
	Lysine degradation	2	38	56	4491	0.05	0.01	Over	0.08	0.13	0.04	M130T80;M277T156
	Arginine and proline metabolism	8	38	71	4491	0.21	0.02	Over	0.00	0.00	0.11	M399T133;M148T390;M175T546;M146T276;M114T47;M146T347;M131T314;M116T272
	Histidine metabolism	3	38	47	4491	0.08	0.01	Over	0.01	0.03	0.06	M148T390;M132T488;M225T422
	Tryptophan metabolism	1	38	83	4491	0.03	0.02	Over	0.51	0.52	0.01	M130T71
	Phenylalanine, tyrosine and tryptophan biosynthesis	1	38	35	4491	0.03	0.01	Over	0.26	0.30	0.03	M259T250
	Caffeine metabolism	1	38	22	4491	0.03	0.00	Over	0.17	0.23	0.05	M151T209
	Neomycin, kanamycin and gentamicin biosynthesis	2	38	81	4491	0.05	0.02	Over	0.15	0.20	0.02	M148T390;M179T176
	Glycolysis / Gluconeogenesis	2	38	31	4491	0.05	0.01	Over	0.03	0.07	0.06	M179T176;M169T341
	Pentose phosphate pathway	1	38	37	4491	0.03	0.01	Over	0.27	0.31	0.03	M179T176
	Pentose and glucuronate interconversions	1	38	59	4491	0.03	0.01	Over	0.40	0.41	0.02	M169T341
	Fructose and mannose metabolism	2	38	55	4491	0.05	0.01	Over	0.08	0.13	0.04	M169T341;M259T250
	Galactose metabolism	2	38	46	4491	0.05	0.01	Over	0.06	0.11	0.04	M179T176;M169T341
	Ascorbate and aldarate metabolism	1	38	57	4491	0.03	0.01	Over	0.39	0.41	0.02	M177T156

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Starch and sucrose metabolism	2	38	37	4491	0.05	0.01	Over	0.04	0.10	0.05	M179T176;M341T388;M377T387
	Amino sugar and nucleotide sugar metabolism	2	38	119	4491	0.05	0.03	Over	0.27	0.31	0.02	M179T176;M308T372;M310T155
	Inositol phosphate metabolism	1	38	47	4491	0.03	0.01	Over	0.33	0.36	0.02	M169T341
	Pyruvate metabolism	1	38	32	4491	0.03	0.01	Over	0.24	0.29	0.03	M71T50
	Glyoxylate and dicarboxylate metabolism	3	38	64	4491	0.08	0.01	Over	0.02	0.05	0.05	M148T390;M147T420;M169T341
	Propanoate metabolism	3	38	41	4491	0.08	0.01	Over	0.00	0.02	0.07	M169T341;M71T50;M103T181
	Butanoate metabolism	2	38	47	4491	0.05	0.01	Over	0.06	0.11	0.04	M148T390;M133T33
	Nitrogen metabolism	2	38	20	4491	0.05	0.00	Over	0.01	0.04	0.10	M148T390;M147T420
	Sulfur metabolism	1	38	34	4491	0.03	0.01	Over	0.25	0.30	0.03	M124T292
	Metabolic pathways	37	38	3101	4491	0.97	0.69	Over	0.00	0.00	0.01	M399T133;M148T390;M179T176;M89T21;M130T80;M132T488;M175T546;M147T420;M171T384;M169T341;M130T268;M793T136;M341T388;M377T387;M124T292;M308T372;M310T155;M267T210;M146T276;M103T401;M151T209;M225T422;M295T252;M277T156;M133T33;M71T50;M188T390;M114T47;M130T318;M210T192;M130T71;M146T347;M174T394;M259T250;M243T238;M177T156;M199T37;M131T314;M116T272
	Carbon metabolism	4	38	112	4491	0.11	0.02	Over	0.01	0.05	0.04	M148T390;M89T21;M132T488;M169T341
	2-Oxocarboxylic acid metabolism	6	38	144	4491	0.16	0.03	Over	0.00	0.01	0.04	M148T390;M89T21;M130T80;M132T488;M130T268;M188T390
	Fatty acid metabolism	1	38	122	4491	0.03	0.03	Under	0.65	0.66	0.01	M103T401
	Biosynthesis of amino acids	11	38	128	4491	0.29	0.03	Over	0.00	0.00	0.09	M399T133;M148T390;M89T21;M130T80;M132T488;M175T546;M147T420;M169T341;M130T268;M277T156;M188T390
	Nucleotide metabolism	3	38	58	4491	0.08	0.01	Over	0.01	0.04	0.05	M147T420;M267T210;M151T209
	Biosynthesis of cofactors	5	38	328	4491	0.13	0.07	Over	0.14	0.20	0.02	M399T133;M148T390;M132T488;M147T420;M210T192
	Biosynthesis of nucleotide sugars	1	38	200	4491	0.03	0.04	Under	0.82	0.82	0.01	M308T372;M310T155
	Fatty acid biosynthesis	2	38	58	4491	0.05	0.01	Over	0.09	0.14	0.03	M103T401;M199T37
	Primary bile acid biosynthesis	1	38	47	4491	0.03	0.01	Over	0.33	0.36	0.02	M124T292
	Glycerolipid metabolism	2	38	38	4491	0.05	0.01	Over	0.04	0.10	0.05	M171T384;M169T341
	Glycerophospholipid metabolism	3	38	56	4491	0.08	0.01	Over	0.01	0.04	0.05	M171T384;M169T341;M793T136
	Arachidonic acid metabolism	1	38	79	4491	0.03	0.02	Over	0.49	0.51	0.01	M793T136
	Linoleic acid metabolism	1	38	29	4491	0.03	0.01	Over	0.22	0.27	0.03	M793T136
	alpha-Linolenic acid metabolism	1	38	44	4491	0.03	0.01	Over	0.31	0.35	0.02	M793T136
	Vitamin B6 metabolism	1	38	29	4491	0.03	0.01	Over	0.22	0.27	0.03	M147T420
	Nicotinate and nicotinamide metabolism	2	38	55	4491	0.05	0.01	Over	0.08	0.13	0.04	M132T488;M169T341
	Pantothenate and CoA biosynthesis	1	38	30	4491	0.03	0.01	Over	0.23	0.27	0.03	M132T488
	Biotin metabolism	1	38	29	4491	0.03	0.01	Over	0.22	0.27	0.03	M130T80
	Porphyrin metabolism	2	38	148	4491	0.05	0.03	Over	0.36	0.38	0.01	M148T390;M210T192
	beta-Alanine metabolism	4	38	32	4491	0.11	0.01	Over	0.00	0.00	0.13	M132T488;M146T276;M103T401;M225T422
	Taurine and hypotaurine metabolism	3	38	24	4491	0.08	0.01	Over	0.00	0.01	0.13	M148T390;M89T21;M124T292
	Selenocompound metabolism	1	38	27	4491	0.03	0.01	Over	0.21	0.26	0.04	M89T21
	D-Amino acid metabolism	8	38	69	4491	0.21	0.02	Over	0.00	0.00	0.12	M148T390;M89T21;M130T80;M132T488;M175T546;M147T420;M188T390;M130T318
	Glutathione metabolism	2	38	38	4491	0.05	0.01	Over	0.04	0.10	0.05	M148T390;M146T276
	Terpenoid backbone biosynthesis	1	38	46	4491	0.03	0.01	Over	0.32	0.36	0.02	M295T252
	Purine metabolism	3	38	101	4491	0.08	0.02	Over	0.05	0.11	0.03	M147T420;M267T210;M151T209

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Pyrimidine metabolism	3	38	66	4491	0.08	0.01	Over	0.02	0.05	0.05	M147T420;M103T401;M243T238
	Carbohydrate digestion and absorption	2	38	27	4491	0.05	0.01	Over	0.02	0.06	0.07	M179T176;M341T388;M377T387
	Protein digestion and absorption	7	38	47	4491	0.18	0.01	Over	0.00	0.00	0.15	M148T390;M89T21;M130T80;M132T488;M175T546;M147T420;M130T268
	Bile secretion	2	38	97	4491	0.05	0.02	Over	0.20	0.26	0.02	M179T176;M146T276
	Mineral absorption	4	38	29	4491	0.11	0.01	Over	0.00	0.00	0.14	M179T176;M89T21;M147T420;M130T268
	Insulin signaling pathway	1	38	4	4491	0.03	0.00	Over	0.03	0.08	0.25	M179T176
	Insulin secretion	1	38	12	4491	0.03	0.00	Over	0.10	0.14	0.08	M179T176
	Prolactin signaling pathway	1	38	11	4491	0.03	0.00	Over	0.09	0.14	0.09	M179T176
	Glucagon signaling pathway	1	38	26	4491	0.03	0.01	Over	0.20	0.26	0.04	M179T176
	Circadian entrainment	1	38	9	4491	0.03	0.00	Over	0.07	0.13	0.11	M148T390
	Proximal tubule bicarbonate reclamation	2	38	17	4491	0.05	0.00	Over	0.01	0.04	0.12	M148T390;M147T420
	Long-term potentiation	1	38	7	4491	0.03	0.00	Over	0.06	0.11	0.14	M148T390
	Synaptic vesicle cycle	1	38	12	4491	0.03	0.00	Over	0.10	0.14	0.08	M148T390
	Retrograde endocannabinoid signaling	2	38	19	4491	0.05	0.00	Over	0.01	0.04	0.11	M148T390;M793T136
	Glutamatergic synapse	2	38	8	4491	0.05	0.00	Over	0.00	0.01	0.25	M148T390;M147T420
	GABAergic synapse	2	38	9	4491	0.05	0.00	Over	0.00	0.01	0.22	M148T390;M147T420
	Long-term depression	1	38	9	4491	0.03	0.00	Over	0.07	0.13	0.11	M148T390
	Taste transduction	3	38	32	4491	0.08	0.01	Over	0.00	0.01	0.09	M148T390;M179T176;M341T388;M377T387
cluster 5	Sphingolipid signaling pathway	3	19	15	4491	0.16	0.00	Over	0.00	0.00	0.20	M268T158;M300T35;M302T57
	cAMP signaling pathway	3	19	25	4491	0.16	0.01	Over	0.00	0.00	0.12	M117T93;M268T158;M146T368
	Choline metabolism in cancer	2	19	11	4491	0.11	0.00	Over	0.00	0.02	0.18	M104T257_2;M524T181
	Glycerophospholipid metabolism	3	19	56	4491	0.16	0.01	Over	0.00	0.02	0.05	M104T257_2;M146T368;M524T181
	Nucleotide metabolism	3	19	58	4491	0.16	0.01	Over	0.00	0.02	0.05	M268T158;M112T187;M306T250
	Sphingolipid metabolism	2	19	35	4491	0.11	0.01	Over	0.01	0.09	0.06	M300T35;M302T57
	Apoptosis	1	19	4	4491	0.05	0.00	Over	0.02	0.11	0.25	M300T35
	Glycine, serine and threonine metabolism	2	19	48	4491	0.11	0.01	Over	0.02	0.11	0.04	M143T306;M132T337
	ABC transporters	3	19	138	4491	0.16	0.03	Over	0.02	0.11	0.02	M268T158;M306T250;M136T336
	Neuroactive ligand-receptor interaction	2	19	53	4491	0.11	0.01	Over	0.02	0.11	0.04	M268T158;M146T368
	Regulation of actin cyto-skeleton	1	19	5	4491	0.05	0.00	Over	0.02	0.11	0.20	M146T368
	Lysine degradation	2	19	56	4491	0.11	0.01	Over	0.02	0.11	0.04	M117T93;M118T373
	Glyoxylate and dicarboxylate metabolism	2	19	64	4491	0.11	0.01	Over	0.03	0.12	0.03	M117T93;M143T306
	Nicotine addiction	1	19	7	4491	0.05	0.00	Over	0.03	0.12	0.14	M146T368
	Morphine addiction	1	19	8	4491	0.05	0.00	Over	0.03	0.12	0.13	M268T158
	D-Amino acid metabolism	2	19	69	4491	0.11	0.02	Over	0.03	0.12	0.03	M118T373;M133T173
	Arginine and proline me-tabolism	2	19	71	4491	0.11	0.02	Over	0.04	0.12	0.03	M132T337;M118T373
	GABAergic synapse	1	19	9	4491	0.05	0.00	Over	0.04	0.12	0.11	M117T93
	Necroptosis	1	19	10	4491	0.05	0.00	Over	0.04	0.12	0.10	M300T35
	cGMP-PKG signaling pathway	1	19	10	4491	0.05	0.00	Over	0.04	0.12	0.10	M268T158
	Alcoholism	1	19	10	4491	0.05	0.00	Over	0.04	0.12	0.10	M268T158
	Oxidative phosphorylation	1	19	12	4491	0.05	0.00	Over	0.05	0.12	0.08	M117T93
	Insulin secretion	1	19	12	4491	0.05	0.00	Over	0.05	0.12	0.08	M146T368
	Synaptic vesicle cycle	1	19	12	4491	0.05	0.00	Over	0.05	0.12	0.08	M146T368

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Cholinergic synapse	1	19	12	4491	0.05	0.00	Over	0.05	0.12	0.08	M146T368
	Gastric acid secretion	1	19	14	4491	0.05	0.00	Over	0.06	0.12	0.07	M146T368
	Regulation of lipolysis in adipocytes	1	19	14	4491	0.05	0.00	Over	0.06	0.12	0.07	M268T158
	Pancreatic secretion	1	19	15	4491	0.05	0.00	Over	0.06	0.12	0.07	M146T368
	Bile secretion	2	19	97	4491	0.11	0.02	Over	0.06	0.12	0.02	M407T218;M146T368
	Vascular smooth muscle contraction	1	19	16	4491	0.05	0.00	Over	0.07	0.12	0.06	M268T158
	Purine metabolism	2	19	101	4491	0.11	0.02	Over	0.07	0.12	0.02	M268T158;M306T250
	Salivary secretion	1	19	17	4491	0.05	0.00	Over	0.07	0.12	0.06	M146T368
	Renin secretion	1	19	17	4491	0.05	0.00	Over	0.07	0.12	0.06	M268T158
	Insulin resistance	1	19	19	4491	0.05	0.00	Over	0.08	0.13	0.05	M204T297
	Carbon metabolism	2	19	112	4491	0.11	0.02	Over	0.08	0.13	0.02	M117T93;M143T306
	Citrate cycle (TCA cycle)	1	19	20	4491	0.05	0.00	Over	0.08	0.13	0.05	M117T93
	Efferocytosis	1	19	21	4491	0.05	0.00	Over	0.09	0.14	0.05	M524T181
	Ether lipid metabolism	1	19	25	4491	0.05	0.01	Over	0.10	0.15	0.04	M104T257_2
	Parkinson disease	1	19	26	4491	0.05	0.01	Over	0.10	0.15	0.04	M268T158
	Glucagon signaling pathway	1	19	26	4491	0.05	0.01	Over	0.10	0.15	0.04	M117T93
	Alanine, aspartate and glutamate metabolism	1	19	28	4491	0.05	0.01	Over	0.11	0.16	0.04	M117T93
	Linoleic acid metabolism	1	19	29	4491	0.05	0.01	Over	0.12	0.16	0.03	M279T36
	Pathways of neurodegeneration - multiple diseases	1	19	32	4491	0.05	0.01	Over	0.13	0.17	0.03	M146T368
	Pyruvate metabolism	1	19	32	4491	0.05	0.01	Over	0.13	0.17	0.03	M117T93
	Taste transduction	1	19	32	4491	0.05	0.01	Over	0.13	0.17	0.03	M146T368
	Sulfur metabolism	1	19	34	4491	0.05	0.01	Over	0.13	0.17	0.03	M117T93
	Central carbon metabolism in cancer	1	19	37	4491	0.05	0.01	Over	0.15	0.18	0.03	M117T93
	Pentose phosphate pathway	1	19	37	4491	0.05	0.01	Over	0.15	0.18	0.03	M143T306
	Glycerolipid metabolism	1	19	38	4491	0.05	0.01	Over	0.15	0.18	0.03	M143T306
	Propanoate metabolism	1	19	41	4491	0.05	0.01	Over	0.16	0.19	0.02	M117T93
	Butanoate metabolism	1	19	47	4491	0.05	0.01	Over	0.18	0.21	0.02	M117T93
	Primary bile acid biosynthesis	1	19	47	4491	0.05	0.01	Over	0.18	0.21	0.02	M407T218
	Phenylalanine metabolism	1	19	49	4491	0.05	0.01	Over	0.19	0.21	0.02	M117T93
	Nicotinate and nicotinamide metabolism	1	19	55	4491	0.05	0.01	Over	0.21	0.23	0.02	M117T93
	Steroid biosynthesis	1	19	57	4491	0.05	0.01	Over	0.22	0.23	0.02	M397T68
	Pyrimidine metabolism	1	19	66	4491	0.05	0.01	Over	0.25	0.26	0.02	M112T187
	Biosynthesis of unsaturated fatty acids	1	19	74	4491	0.05	0.02	Over	0.27	0.28	0.01	M279T36
	Tyrosine metabolism	1	19	78	4491	0.05	0.02	Over	0.28	0.29	0.01	M117T93
	Metabolic pathways	14	19	3101	4491	0.74	0.69	Over	0.44	0.44	0.00	M117T93;M268T158;M143T306;M132T337;M300T35;M112T187;M306T250;M118T373;M133T173;M407T218;M302T57;M279T36;M165T244;M397T68
cluster 6	Mineral absorption	2	11	29	4491	0.18	0.01	Over	0.00	0.02	0.07	M188T191;M166T263
	Pantothenate and CoA biosynthesis	2	11	30	4491	0.18	0.01	Over	0.00	0.02	0.07	M111T77;M202T52
	beta-Alanine metabolism	2	11	32	4491	0.18	0.01	Over	0.00	0.02	0.06	M111T77;M202T52
	Phenylalanine, tyrosine and tryptophan biosynthesis	2	11	35	4491	0.18	0.01	Over	0.00	0.02	0.06	M188T191;M166T263
	Central carbon metabolism in cancer	2	11	37	4491	0.18	0.01	Over	0.00	0.02	0.05	M188T191;M166T263
	Vitamin digestion and absorption	2	11	42	4491	0.18	0.01	Over	0.00	0.02	0.05	M455T30;M202T52

Clusters	Pathway Name	Test	TestAll	Ref	RefAll	Test per	Ref per	Over/ Under	Pvalue	FDR	Rich-Factor	Metabolite Name
	Protein digestion and absorption	2	11	47	4491	0.18	0.01	Over	0.01	0.03	0.04	M188T191;M166T263
	Aminoacyl-tRNA biosynthesis	2	11	52	4491	0.18	0.01	Over	0.01	0.03	0.04	M188T191;M166T263
	African trypanosomiasis	1	11	8	4491	0.09	0.00	Over	0.02	0.07	0.13	M188T191
	Prostate cancer	1	11	11	4491	0.09	0.00	Over	0.03	0.09	0.09	M271T134
	Biosynthesis of amino acids	2	11	128	4491	0.18	0.03	Over	0.04	0.11	0.02	M188T191;M166T263
	Biosynthesis of cofactors	3	11	328	4491	0.27	0.07	Over	0.04	0.11	0.01	M455T30;M188T191;M202T52
	ABC transporters	2	11	138	4491	0.18	0.03	Over	0.04	0.11	0.01	M166T263;M527T440
	2-Oxocarboxylic acid metabolism	2	11	144	4491	0.18	0.03	Over	0.05	0.11	0.01	M188T191;M166T263
	Riboflavin metabolism	1	11	24	4491	0.09	0.01	Over	0.06	0.12	0.04	M455T30
	Ovarian steroidogenesis	1	11	24	4491	0.09	0.01	Over	0.06	0.12	0.04	M271T134
	Carbohydrate digestion and absorption	1	11	27	4491	0.09	0.01	Over	0.06	0.12	0.04	M527T440
	Pathways in cancer	1	11	31	4491	0.09	0.01	Over	0.07	0.13	0.03	M271T134
	Fatty acid elongation	1	11	40	4491	0.09	0.01	Over	0.09	0.16	0.03	M257T35_1
	Serotonergic synapse	1	11	42	4491	0.09	0.01	Over	0.10	0.16	0.02	M188T191
	Glycine, serine and threonine metabolism	1	11	48	4491	0.09	0.01	Over	0.11	0.17	0.02	M188T191
	Phenylalanine metabolism	1	11	49	4491	0.09	0.01	Over	0.11	0.17	0.02	M166T263
	Fatty acid degradation	1	11	50	4491	0.09	0.01	Over	0.12	0.17	0.02	M257T35_1
	Nucleotide metabolism	1	11	58	4491	0.09	0.01	Over	0.13	0.17	0.02	M111T77
	Fatty acid biosynthesis	1	11	58	4491	0.09	0.01	Over	0.13	0.17	0.02	M257T35_1
	Pentose and glucuronate interconversions	1	11	59	4491	0.09	0.01	Over	0.14	0.17	0.02	M149T87
	Pyrimidine metabolism	1	11	66	4491	0.09	0.01	Over	0.15	0.18	0.02	M111T77
	D-Amino acid metabolism	1	11	69	4491	0.09	0.02	Over	0.16	0.18	0.01	M166T263
	Biosynthesis of unsaturated fatty acids	1	11	74	4491	0.09	0.02	Over	0.17	0.19	0.01	M257T35_1
	Tryptophan metabolism	1	11	83	4491	0.09	0.02	Over	0.19	0.20	0.01	M188T191
	Steroid hormone biosynthesis	1	11	101	4491	0.09	0.02	Over	0.22	0.24	0.01	M271T134
	Fatty acid metabolism	1	11	122	4491	0.09	0.03	Over	0.26	0.27	0.01	M257T35_1
	Metabolic pathways	9	11	3101	4491	0.82	0.69	Over	0.29	0.29	0.00	M455T30;M188T191;M166T263;M111T77;M257T35_1;M202T52;M117T444;M271T134;M271T36

Table S4. Correlation analysis between key metabolites and clinical parameters in patients with CRSwNP or asthma.

Diseases	Metabolite	Clinical	Cor	P-value
CRSwNP	N-(8Z,11Z,15Z-eicosatrienoyl)	WBC___X10^9/L	0.133766234	0.324724
	N-(8Z,11Z,16Z-eicosatrienoyl)	N:___%	0.075703202	0.579215942
	N-(8Z,11Z,17Z-eicosatrienoyl)	L:___%	-0.043134239	0.752265312
	N-(8Z,11Z,18Z-eicosatrienoyl)	EOS%	0.070555259	0.605349185
	N-(8Z,11Z,19Z-eicosatrienoyl)	EOS:___X10^9/L	0.11313531	0.406424461
	N-(8Z,11Z,20Z-eicosatrienoyl)	Number of EOS/HFP	0.039749133	0.771157393
	N-(8Z,11Z,21Z-eicosatrienoyl)	Nasal endoscopy score	-0.077064448	0.572392747
	N-(8Z,11Z,22Z-eicosatrienoyl)	Lund-Mackay CT score	0.190571554	0.1634191
	N-(8Z,11Z,20Z-eicosatrienoyl)	FVCex%	-0.044149591	0.746626142
	N-(8Z,11Z,21Z-eicosatrienoyl)	FEV1%	-0.07849645	0.565255201
	N-(8Z,11Z,22Z-eicosatrienoyl)	FEV1/FVCex %	-0.133586056	0.326332504
	LTF4	WBC___X109/L	-0.244702666	0.069298205
	LTF4	N:___%	-0.208551215	0.122959397
	LTF4	L:___%	0.087328036	0.522180234
	LTF4	EOS%	0.230202351	0.087853685
	LTF4	EOS:___X10^9/L	0.229075911	0.089461019
	LTF4	Number of EOS/HFP	-0.097031632	0.476822481
	LTF4	Nasal endoscopy score	0.029334436	0.830068402
	LTF4	Lund-Mackay CT score	0.232960976	0.086963037
	LTF4	FVCex%	-0.034916136	0.79835771
	LTF4	FEV1%	-0.013749705	0.919885955
	LTF4	FEV1/FVCex %	-0.066192526	0.627889461
Asthma	N-(8Z,11Z,15Z-eicosatrienoyl)	EOS%	-0.259877185	0.282610623
	N-(8Z,11Z,16Z-eicosatrienoyl)	EOS X10^9/L	-0.139534897	0.568863303
	N-(8Z,11Z,17Z-eicosatrienoyl)	IgE(IU/ml)	-0.175	0.532030437
	N-(8Z,11Z,18Z-eicosatrienoyl)	FEV1%	0.110720733	0.651811027
	N-(8Z,11Z,19Z-eicosatrienoyl)	FVCex %	-0.035133979	0.886454541
	N-(8Z,11Z,20Z-eicosatrienoyl)	FEV1/FVCex %	0.169596044	0.487607416
	N-(8Z,11Z,21Z-eicosatrienoyl)	FeNO (ppb)	0.598460208	0.023759215
	N-(8Z,11Z,22Z-eicosatrienoyl)	FnNO (ppb)	0.450549451	0.124700834
	LTF4	EOS%	0.017559269	0.943120829
	LTF4	EOS X10^9/L	0.131636695	0.591140499
	LTF4	IgE(IU/ml)	-0.042857143	0.882795761
	LTF4	FEV1%	0.120386829	0.623482371
	LTF4	FVCex %	-0.121212226	0.621085949
	LTF4	FEV1/FVCex %	0.463093861	0.045852793
	LTF4	FeNO (ppb)	0.180418151	0.537087371
	LTF4	FnNO (ppb)	0.313186813	0.297341476

Table S5. CV results for key metabolites.

ID	group	Mean	SD	CV
N-(8Z,11Z,14Z-eicosatrienoyl)	Control vs Asthma vs CRSwNP (upper airway)	17237.54188	16013.51986	0.928990918
N-(8Z,11Z,15Z-eicosatrienoyl)	Control vs Asthma vs CRSwNP (lower airway)	15604.35025	15936.83908	1.021307445
N-(8Z,11Z,16Z-eicosatrienoyl)	Control (upper airway)	23328.82756	18775.25377	0.804809145
N-(8Z,11Z,17Z-eicosatrienoyl)	Asthma (upper airway)	7239.415022	4357.324462	0.601889027
N-(8Z,11Z,18Z-eicosatrienoyl)	CRSwNP (upper airway)	13458.99908	11871.63536	0.882059304
N-(8Z,11Z,19Z-eicosatrienoyl)	Control (lower airway)	21850.77149	20213.52323	0.925071375
N-(8Z,11Z,20Z-eicosatrienoyl)	CRSwNP (lower airway)	11548.67441	9125.202382	0.790151498
N-(8Z,11Z,21Z-eicosatrienoyl)	Asthma (lower airway)	7076.708138	3343.781911	0.472505273
LTF4	Control vs Asthma vs CRSwNP (upper airway)	884.3033795	1703.620802	1.926511695
LTF4	Control vs Asthma vs CRSwNP (lower airway)	2090.861805	6970.716107	3.333896142
LTF4	Control (upper airway)	613.9055926	488.4522349	0.79564715
LTF4	Asthma (upper airway)	1365.755417	4459.725688	3.265391177
LTF4	CRSwNP (upper airway)	1041.286101	1052.317989	1.010594483
LTF4	Control (lower airway)	981.8890197	1203.441866	1.225639397
LTF4	CRSwNP (lower airway)	1990.253969	3601.223102	1.809428926
LTF4	Asthma (lower airway)	5937.186179	17210.60499	2.898781421