Exploratory analysis of untargeted metabolomics datasets from U-BIOPRED project

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Abstract

Introduction Asthma is a heterogeneous disease with a complex pathophysiology. There is an urge to improve the understanding of asthma mechanisms and disease management at the molecular level. This study aims to identify the most altered features associated with asthma, followed by discovering asthma-related urinary metabotypes and differentiators.

Methods From the cross-sectional U-BIOPRED project, adult baseline urine samples were collected from healthy participants (*n=95*), patients with mild-to-moderate asthma (*n=84*), non-smoking severe asthmatics (*n=293*), and smoking/ex-smoking severe asthmatics (*n=101*). Untargeted metabolomics data were measured using high-resolution mass spectrometry. Univariate analysis and consensus clustering methods were used for statistical analysis.

Results From two complementary HILIC methods, 247 compounds were tentatively identified, composed of 205 metabolites from ZIC-HILIC positive ionization mode and 42 from negative ionization mode. Four subgroups with different metabolic patterns were classified. Endogenous steroid metabolites, caffeine metabolites, and carnitine species differentiated asthmatic subgroups from healthy controls.

Conclusions A total of 233 unique urinary metabolites were identified from two complementary ZIC-HILIC ionization modes. Although the unsupervised clustering algorithm yielded subgroups with different metabotypes, the differentiated metabolites are not specific enough to conclude any phenotypes or molecular descriptors.

Layman's summary

Asthma is a common airway disease with significant health consequences for both children and adults. The onset of asthma is associated with body condition, smoking, or exposure to environmental risk factors. Clinical diagnosis of asthma is based on a series of symptoms patients present instead of standard diagnostic tests. Without considering individual differences, disease management outcomes are hampered by unexpected adverse events of medications and uncontrollable disease progression. Therefore, there is an urge to find molecular markers that can consistently distinguish asthmatics subtypes.

Urinary samples measured by untargeted mass spectrometry-based metabolomics provide a snapshot of global metabolites. As final products of biochemical progress in the human body, changes in urinary abundance deliver information about systemic conditions, including disease, diet, environment, and drugs. This advantage aids in the sub-phenotype identification of asthma due to its complex etiologies.

U-BIOPRED (Unbiased BIOmarkers in the PREDiction of respiratory disease outcomes) is a large-scale pan-European clinical project aiming at asthma sub-phenotype identification via multi-omics platforms. Adult and paediatric patients were recruited from multiple centers, and samples of various matrices were collected at different time points.

This study aims to get the most altered metabolites identified from urinary untargeted metabolomics datasets and further discover asthma-related urinary metabotypes and differentiators.

The U-BIOPRED project collected 573 adult baseline urinary samples from four well-characterized cohorts: healthy participants, mild-to-moderate asthmatics, non-smoking severe asthmatics, and smoking/ex-smoking severe asthmatics. All the statistics were performed using R.

From two complementary HILIC methods, 247 metabolites were tentatively identified, composed of 205 metabolites from ZIC-HILIC positive ionization mode and 42 from negative ionization mode. Four subgroups with different metabolic patterns were characterized. Endogenous steroid metabolites, caffeine metabolites, and carnitine species differentiated asthmatic subgroups from healthy controls.

In summary, 233 unique urinary metabolites were tentatively identified from two complementary ZIC-HILIC ionization modes. Although the unsupervised clustering algorithm yielded clusters with different metabotypes, the differentiated metabolites are not specific enough to conclude any phenotypes or molecular descriptors.

1. Introduction

Asthma is one of the most common non-communicable diseases with significant health consequences for both children and adults (1). Around 300 million asthma patients worldwide manifest the symptoms of wheezing, shortness of breath, and airway obstruction (2, 3). The interactions between genetic susceptibility, host factors, and environmental exposures make asthma a complex multifactorial heterogeneous disorder (4).

However, clinical diagnosis of asthma is based on patients' presentation with respiratory symptoms, previous medical records, and tests for variability and atopy (5). Although there are several clinical phenotypes of asthma, these descriptive, symptom-focused approaches exclude the heterogeneous influence of individuals. Consequently, patients diagnosed with the same asthma phenotype respond diversely to treatment. In particular, severe asthma patients often suffer from adverse outcomes such as side effects from medications, hospitalization, or even near-fatal events (6-9).

Recent efforts have been put into deconstructing asthma and categorizing patients at the molecular level to find well-defined biomarkers. Untargeted mass spectrometry-based metabolomics using accessible biofluids provides global metabolite profiling of the body (10). As the end products of biochemical reactions, the fluctuation of circulation metabolites reflects the interactive responses between disease status, dietary habits, environmental factors, and therapeutic intervention (11), which is suitable for asthma sub-phenotyping.

U-BIOPRED (Unbiased BIOmarkers in the PREDiction of respiratory disease outcomes) study is a large pan-European project aiming at asthma sub-phenotype identification via integrating multi-omics platforms to increase molecular resolution (12-14). The projects recruited both adult and paediatric patients, and multiple matrices (urine, blood, and sputum) were collected at the cross-sectional and longitudinal visits.

We hypothesize that asthma patients exhibit distinct urinary metabotypes, and the identification of molecular descriptors with sufficient resolution can characterize multiple asthma subgroups. This study aims to identify the most altered metabolites from urinary all-feature datasets and discover asthma-related urinary metabotypes and differentiators.

Abbreviations used

U-BIOPRED: Unbiased biomarkers for the prediction of respiratory diseases outcomes
ZHP: ZIC-HILIC positive ionization mode
ZHN: ZIC-HILIC negative ionization mode
CDF: Cumulative distribution function
OCS: Oral corticosteroids

2. Methods

Study subjects and design

Urine samples were prospectively collected for the cross-sectional U-BIOPRED study (14). *573* adult baseline urinary samples **(FIGURE E1 and TABLE E1)** were classified according to international guidelines on severe asthma with the following groups: healthy participants (HC; *n=95*), mild-to-moderate asthmatics (MMA; *n=84*), non-smoking severe asthmatics (SAns; *n=293*), and smoking/ex-smoking severe asthmatics (SAs; *n=101*).

Mass spectrometry analysis

Metabolomics data were acquired by liquid chromatography-high resolution mass spectrometry (LC-HRMS) employing the all-ion fragmentation (AIF) approach (15). Urine samples were randomized and normalized with specific gravity (SG) to reduce matrix effects (15). Two LC-MS ionization modes (ZHP (ZIC-HILIC positive) and ZHN (ZIC-HILIC negative)) were applied, and the acquired data were pre-processed using the method described before (15, 16).

The datasets used in this study are different from annotated datasets in terms of containing unknown peaks that were processed at the feature level (m/z and its corresponding RT (retention time)). Other than that, all-feature datasets were exported with additional filtering steps (16). For metabolite identification, accurate mass, RT, MS/MS spectrum, and product/precursor ion intensity ratios are considered. Three levels were presented in this study: (i) AMRT and MS/MS confirmed, (ii) AMRT confirmed, and (iii) MS/MS confirmed.

Statistical analysis

Statistical analysis and visualization were performed in R.

Univariate statistics

Relative abundances of features were non-normally distributed (Lilliefors test). Therefore, non-parametric univariate statistical tests were subsequently used. The Kruskal-Wallis test was used for multiple-group comparison, followed by a Tukey *post hoc* pairwise comparison test. Storey positive false discovery rate (FDR) was calculated to correct p values for multiple testing. Median fold change and confidence intervals were estimated using bootstrapping (500 iterations).

Consensus cluster analysis

Consensus clustering is a method for unsupervised subtype discovery and sample classification using high-dimensional data. Consensus clustering was performed using the "ConsensusClusterPlus" package in R.

Metabolites with more than 20% missing values were removed for downstream analysis, and the rest missing values were imputed with 0.5 times the minimum value of each corresponding metabolite. A matrix of *478* asthmatics (*293* SAns, *101* SAs, and *84* MMA) x

annotated metabolites were input to the consensus clustering algorithm after log2 transformation and Z-scored standardization.

The similarity between subjects was described by calculating Euclidean distance, and the partitioning around the medoids (PAM) algorithm was used for clustering. The clustering was repeated 1000 times, removing randomly 10% of the subjects at each iteration.

Classification analysis with variable selection and Random Forest

The "Boruta" package (17), a wrapper built around the Random Forest classification method, was used to identify attributes relevant for classification. The algorithm creates a shadow attribute of each independent variable and shuffles the added attributes to remove possible correlations. The maximum Z score of shadow attributes is defined as the threshold value. Original variables with Z scores higher than the threshold are deemed "important" ($p<0.01$). The procedure was repeated 1,000 times.

3. Results

291 features were selected for metabolite annotation

15,583 and 16,934 features were obtained separately from the ZIC-HILIC positive and negative ionization mode. In each dataset, we aimed to limit the scope from more than 15,000 features to 100-150 features for metabolite annotation. Due to the minor difference between MMA and HC, the selection emphases on the comparison between severe asthmatics and healthy volunteers, as well as the effect of smoking. The features were considered consistently differentially abundant when their respective p values were smaller than 0.05 (0.001 for features obtained by the ZHN method) and fold change larger than two times in the comparison between SAns vs HC, SAs vs HC, and SAns vs SAs **(FIGURE 1 and E2)**. Taken together, 291 features (123 from A.ZHP and 168 from B.ZHN) were significantly altered between multiple comparisons.

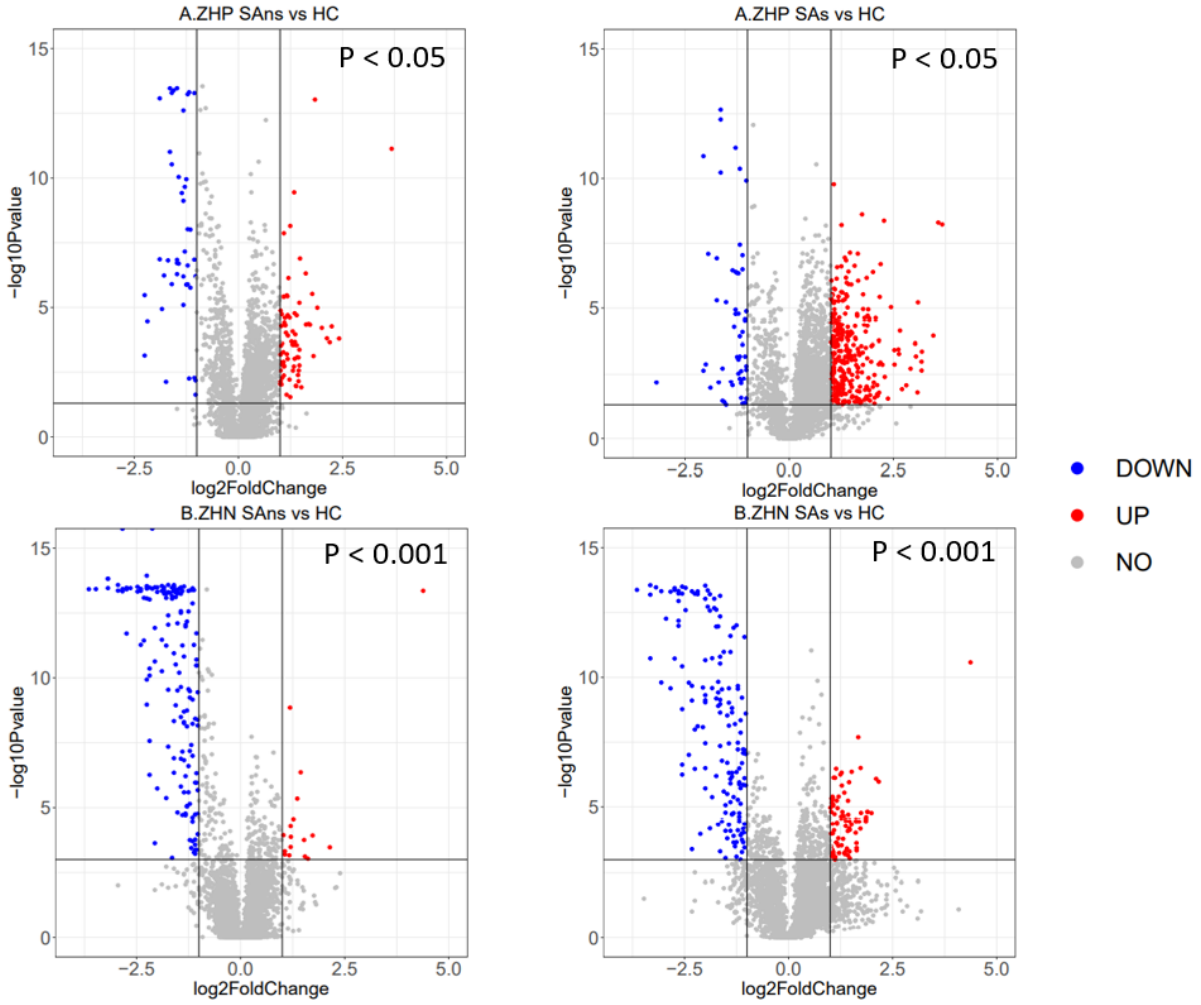

FIGURE 1. Volcano plots of pairwise comparisons in U-BIOPRED measured by ZHP and ZHN methods. The volcano plots show feature abundance compared with healthy controls. The data point above the significance threshold ($p < 0.05$ for ZHP, $p < 0.001$ for ZHN, and fold change > 2) are marked in blue (lower abundance in asthmatics) and red (higher abundance in asthmatics), and others are marked in gray (not significant). HC = healthy non-smoking controls; SAns = non-smokers with severe asthma; SAs = smokers or ex-smokers with severe asthma; ZHP = ZIC-HILIC positive method; ZHN = ZIC-HILIC negative method.

247 urinary metabolites were tentatively identified

Including annotated metabolites in improved in-house libraries as well as 291 altered features selected above, 205 metabolites were identified from the ZHP dataset, of which 118 were AM, RT, and MS/MS matched, 40 were AM and RT matched, and 47 were AM matched with MS-FINDER. The final ZHN dataset compromised 42 metabolites (14 AMRT-MS/MS, 9 AMRT only, 19 MS only). In total, compared to annotated datasets generated in 2016, where 90 metabolites were pooled from the library (17) **(FIGURE E4)**, 247 compounds (233 unique) were tentatively identified at different identification levels, with 14 metabolites detected by both methods **(FIGURE E3)**.

Taken together, 285 metabolites were tentatively annotated. Five metabolites were removed due to missing values more than 20%, and 280 metabolites were considered for downstream analysis.

Identification of metabolite-driven subgroups of asthma

Clusters

To identify metabolite-driven subgroups of asthma, a consensus clustering algorithm was applied to assess the stability of a number of potential number of clusters (2 to 10). This resulted in the separation of 3 or 4 stable groups after resampling, as defined by well-defined squares within the consensus matrix **(FIGURE 2A)**, a flat middle segment of consensus CDF (cumulative distribution function) **(FIGURE 2B)**, an elbow point in the delta area of CDF curve **(FIGURE 2C)**, and relative stable quality between subtypes defined from clustering **(FIGURE 2D)**. Although separating into 3 and 4 clusters resulted in similar quality, 4 clusters were chosen for further analysis to allow for a more precise sub-phenotype definition. By applying a classification algorithm, it was possible to identify 101 metabolites (97 unique metabolites) confirmed as important for classifying the four clusters **(FIGURE E5)**.

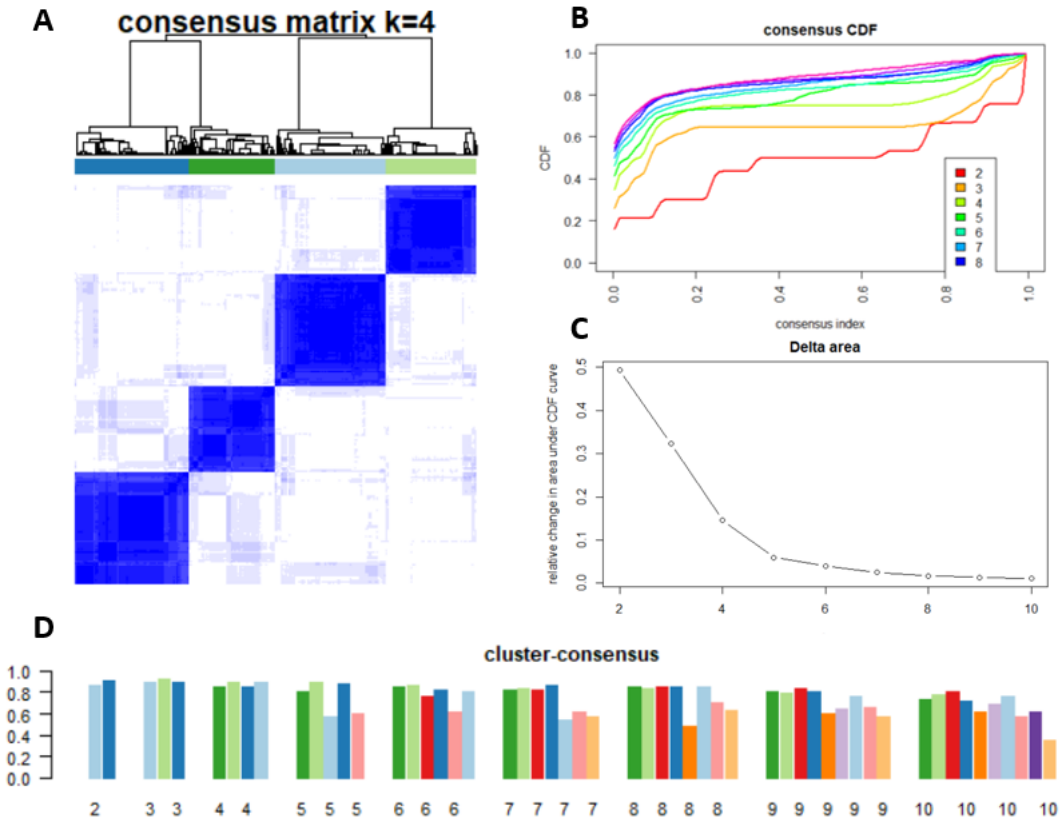

FIGURE 2. Consensus clustering of U-BIOPRED asthmatics. Clustering was applied to U-BIOPRED subjects with asthma (*n=478*) using the input of 280 annotated metabolites. **(A)** Consensus matrices for models with the optimal number of clusters. Four clusters (K=4) were visualized in heatmaps. **(B)** Consensus CDF plot for cluster models of two (K=2) up to ten (K=10) clusters. **(C)** Delta area plot with the relative change in the area under the CDF curve when comparing models with "K" clusters and "K-1" clusters. **(D)** Cluster-consensus plot where, for a given cluster model K, the mean of all pairwise consensus values are higher if subjects are more often clustered together. CDF = cumulative distribution function.

Four-cluster analysis (A1-A4)

The significant clinical variables of the four clusters are listed in **TABLE 1**. Briefly, cluster A1 is composed of patients with moderate-to-severe asthma with poor control. Cluster A2 mainly consists of non-smoking patients (71%) with well-controlled asthma, despite relatively poor lung function amongst subtypes (mean FEV_1, 65.9% of predicted value). Cluster A3 is similar to cluster A1 in terms of lung function, except that the patients were nonsmokers diagnosed with asthma at a younger age. Cluster A4 is mostly composed of female asthmatics patients (71%) experiencing frequent exacerbations despite near-normal lung function and widely receiving OCS (oral corticosteroids) (62%) and anti-IgE (17%) treatment. Although the statistics of the clinical variables were significant, four metabolite-driven clusters are not explicitly associated with any clinical phenotypes of asthma.

TABLE 1. Clinical characteristics of the four metabolite-driven clusters of asthmatics in the U-BIOPRED cohort.

Cluster	A1 (n= 103)	A2 (n= 107)	A3 (n= 135)	A4 (n= 133)	P value
MMA per cluster	14 (14%)	15 (14%)	40 (30%)	15 (11%)	
SA per cluster	89 (86%)	92 (86%)	95 (70%)	118 (89%)	
SAn	60 (58%)	72 (67%)	76 (56%)	85 (64%)	
SAs/ex	29 (28%)	20 (19%)	19 (14%)	33 (25%)	
Age (years)	58 (46 - 64.5)	53 (45 - 59.5)	46 (31.5 - 58)	53 (45 - 62)	<0.001*
Females	52 (50%)	71 (66%)	68 (50%)	94 (71%)	0.001†
Age of Onset OR First Diagnosis (years)	32 (12 - 46.5)	24 (7.75 - 38.2)	16 (6 - 28.5)	28 (11 - 43)	0.001*
Exacerbation number in past year	2 (1 - 3)	1 (0 - 2.75)	2 (0 - 3)	2 (1 - 3)	<0.05*
Smoking status (Non-smoker)	60 (58%)	76 (71%)	105 (78%)	76 (57%)	<0.001*
FEV_1 % (L)	72.2 (52.8 - 86.2)	65.9 (51.2 - 85.6)	73.6 (56.8 - 90.4)	73.2 (56.8 - 88.5)	n.s.*
FEV_1 predicted (L)	2.92 (2.4 - 3.44)	2.78 (2.36 - 3.32)	3.23 (2.76 - 3.78)	2.69 (2.32 - 3.32)	<0.001*
FEV_1 actual (L)	1.94 (1.46 - 2.69)	1.85 (1.36 - 2.47)	2.32 (1.7 - 3.07)	1.94 (1.47 - 2.48)	<0.01*
FEV_1 pre-Salbutamol (L)	1.86 (1.43 - 2.65)	1.86 (1.36 - 2.4)	2.37 (1.62 - 2.94)	1.88 (1.44 - 2.48)	<0.01*
FEV_1 post Salbutamol (L)	2.14 (1.67 - 2.99)	2.12 (1.58 - 2.86)	2.51 (1.9 - 3.2)	2.18 (1.64 - 2.75)	<0.01*
FEV_1/FVC pre-Salbutamol actual ratio	63.3 (52.9 - 70.9)	61.4 (54.3 - 72.7)	67.5 (58.8 - 75.9)	63.4 (54.4 - 75.5)	<0.05*
FEV_1/FVC post Salbutamol actual ratio	67.5 (56 - 75.4)	65.8 (57.9 - 76.7)	72 (63.1 - 80.3)	66.5 (58.3 - 77.2)	<0.05*
Oral corticosteroids	58 (56%)	39 (36%)	51 (38%)	82 (62%)	<0.05*
Anti-IgE therapy	11 (11%)	11 (10%)	10 (7%)	22 (17%)	<0.05*
Inhaled combinations	80 (78%)	85 (79%)	90 (67%)	102 (77%)	<0.001*
Diabetes diagnosed	13 (13%)	14 (13%)	7 (5%)	6 (5%)	<0.05*
Blood Wbcs (x10^3/uL)	8.1 (6.56 - 10.1)	7.7 (5.82 - 9.52)	7.26 (5.85 - 8.62)	7.9 (6.32 - 9.8)	<0.05*
Blood basophils (x10^3/uL)	0.03 (0 - 0.095)	0.03 (0.005 - 0.1)	0.02 (0 - 0.0725)	0.05 (0.01 - 0.1)	<0.05*

FEV = forced expiratory volume; FVC = forced vital capacity; HC = healthy non-smoking controls; SAns = non-smokers with severe asthma; SAs = smokers or ex-smokers with severe asthma.
*Kruskal-Wallis test, unadjusted
†Chi-squared test, unadjusted

Differential metabolite identification for the experimental dataset

Volcano plot analysis **(FIGURE 3)** was used to assess which metabolites differentiated subgroups from healthy participants ($p < 0.05$, fold change > 2). All subtypes showed an elevated abundance of Salbutamol and its metabolites. The metabolites with lower abundance in A1 are six endogenous steroid metabolites. Tetradecadienyl-carnitine (C14:2) is the only carnitine that increased in the metabolite-driven subgroups. For A2, eight endogenous steroid metabolites and two carnitine species (isobar of glutaryl-carnitine (C5:0-OOH) and undecanoyl-carnitine (C11:0)) showed decreased abundance. Two caffeine metabolites (caffeine and dimethylxanthine) and four carnitine species (acetyl−carnitine (C2), propionyl−carnitine (C3:0), undecenoyl−carnitine (C11:1), and isobar of glutaryl-carnitine (C5:0-OOH)) discriminated A3 from healthy participants. In subgroup A4, four unique caffeine metabolites (trigonelline, 2-furoylglycine, 2,3-dihydroxypyridine, xylose) increased more than two times while having ten endogenous steroid metabolites and ten carnitine species decreased.

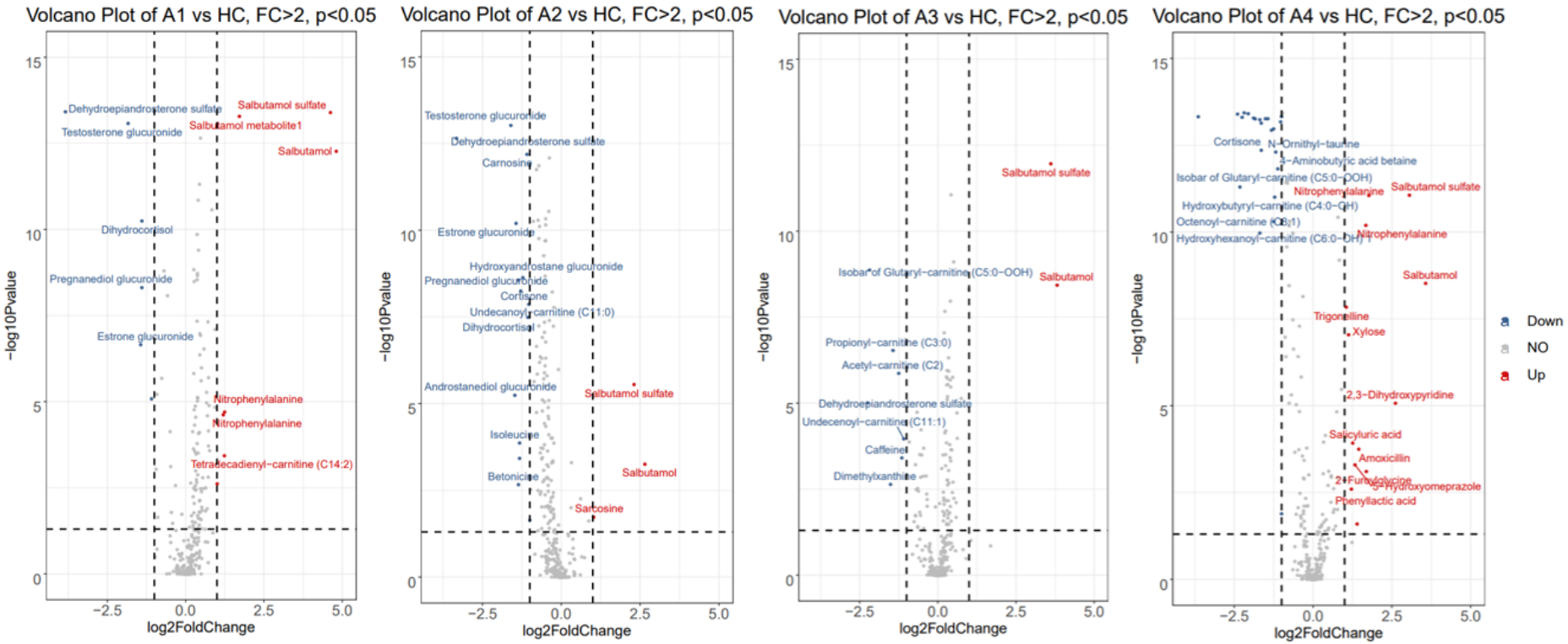

FIGURE 3. Comparisons of metabolic profile between subtypes (A1-A4) and healthy participants. The volcano plots show the abundance of differentiated metabolites compared with HCs. From A1-A4, there are 12, 18, 9, and 30 altered metabolites, respectively. The data points above the significance threshold ($p < 0.05$, foldchange > 2) are marked in blue (lower abundance in subtypes) and red (higher abundance in subtypes), and others are marked in gray (not significant). HC = healthy controls.

4. Discussion

Building upon earlier work in 2016, where 90 metabolites were targeted pooled from the in-house library, annotated metabolites increased to 247 (132 AMRT-MS/MS, 49 AMRT only, and 66 MS only). Consensus clustering analysis yielded four metabolite-driven clusters of asthmatics differentiated by endogenous steroid metabolites, caffeine metabolites, and carnitine species.

The unsupervised classification method usually requires an inner replication (validation dataset) to guarantee confidence and reliability since it confirms the results obtained from the training dataset. However, two problems occurred when performing consensus clustering algorithms.

Firstly, the U-BIOPRED project has defined a formal training/validation split where important clinical variables (asthma severity, gender, and age) were well balanced. In our study, 10 out of 280 metabolites were not balanced (adenosine, NN-dimethyl lysine, nonanoyl-carnitine (C9:0), hexenoyl-carnitine (C6:1), threonine, glucose, galacturonic acid, and pyroglutamylglycine) **(TABLE E4)**. It is noted that energy supply is a common altered metabolism area in asthma studies, and glucose, threonine, and adenosine are involved in different energy metabolic pathways (18). Moreover, these three compounds are at least reported twice as differential metabolites from asthma studies (19), indicating biased results from combining training and validation sets.

Another barrier was mapping the clusters from training and validation sets into sub-phenotypes. Initially, several clusters were classified from the training and validation set separately. Based on the patterns of driving metabolites and clinical characteristics of each subgroup, sub-phenotypes were subsequently mapped. However, no stable sub-phenotypes were yielded from these attempts despite using various sizes of participants (all asthmatics or only severe asthmatics), metabolites (all identified metabolites or excluding caffeine metabolites), and a different number of clusters (2 or 3). Since the mapped sub-phenotypes were similar to that of clustering asthmatics as a whole, results from clustering all asthmatics using 280 metabolites with smaller bias were reported here.

The discriminative role of endogenous steroid metabolites attributes to the oral corticosteroid (OCS) treatment of asthmatics. OCS is an effective and widely used therapy in severe asthma management (20). Long-term external glucocorticoid administration exerts suppressive effects through feedback-inhibition loops, leading to adrenal inefficiency with lower global endogenous steroids (21). Since gender composition affects the level of sex-related steroids such as testosterone and estrone, the influence of sex in metabolite phenotyping remains to be evaluated.

Caffeine, chemically a methylxanthine (1,3,7-trimethylxanthine), is available from natural botanical species and commonly consumed in beverages and foods, such as coffee, tea, energy/soft drinks, chewing gums, and cocoa (22). It is absorbed within 45 minutes in the small intestine and is primarily metabolized in the liver via the isoenzyme CYP1A2 (more than 95%) (23). The caffeine itself can increase the CYP1A2 activity, and the rate of metabolism and elimination is dependent on age, gender, and smoking habit (24, 25). In addition, caffeine is a common ingredient in bronchodilators that modestly improve airway function (22). This

bronchodilator property can be found in three main caffeine products yielded from the first demethylated steps. These primary caffeine metabolites are paraxanthine (1,7-dimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine), of which theophylline is a second-line drug in asthma treatment (26). Caffeine metabolites were not distinguished between clinical cohorts in the U-BIOPRED project **(TABLE E2)**. Considering possible pharmacokinetic disturbances and confounding effects, although several metabolomics studies have reported altered caffeine metabolism in asthma (27, 28), the results should be interpreted with caution.

Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is a conditionally essential nutrient that involves the transport of long-chain fatty acids into the mitochondria matrix, where fatty acid oxidation occurs for energy supply (29). Previously, decreased abundance of acetyl−carnitine (C2) and propionyl−carnitine (C3:0) have been reported in relation to disease severity and are independent of OCS treatment (17). From the 40 carnitine species identified in the current library, this decreasing pattern is partly consistent despite several weak anti-correlation **(FIGURE E6)**, and 33 carnitine species are independent of OCS treatment **(TABLE E3)**. Further investigation is required to illustrate pharmacological variance among the different lengths of side chains and the number of double bonds.

Principal component analysis (PCA) suggests better-separated ellipses of metabolite-driven clusters than clinical cohorts **(FIGURE E7)**. However, the first two principal components only explain 15.2% of the variance, which is insufficient to conclude any discriminative asthma-related metabotypes or differential metabolites.

The current study is unique and represents the large-scale untargeted mass spectrometry-based investigation of the urinary metabolome in adult asthma patients. Certain metabolic pathways were revealed to improve the understanding of the metabotypes of asthma. However, endotype or phenotype identification requires a unifying and consistent clinical and physiological characteristic. The understanding of confounders is not yet comprehensive enough, leaving insufficient molecular resolution for unbiased asthma subtype identification. Although several metabolic signatures are related to asthma sub-phenotyping, it does not achieve all the requirements to form a true endotype or phenotype (30).

5. Supplementary material

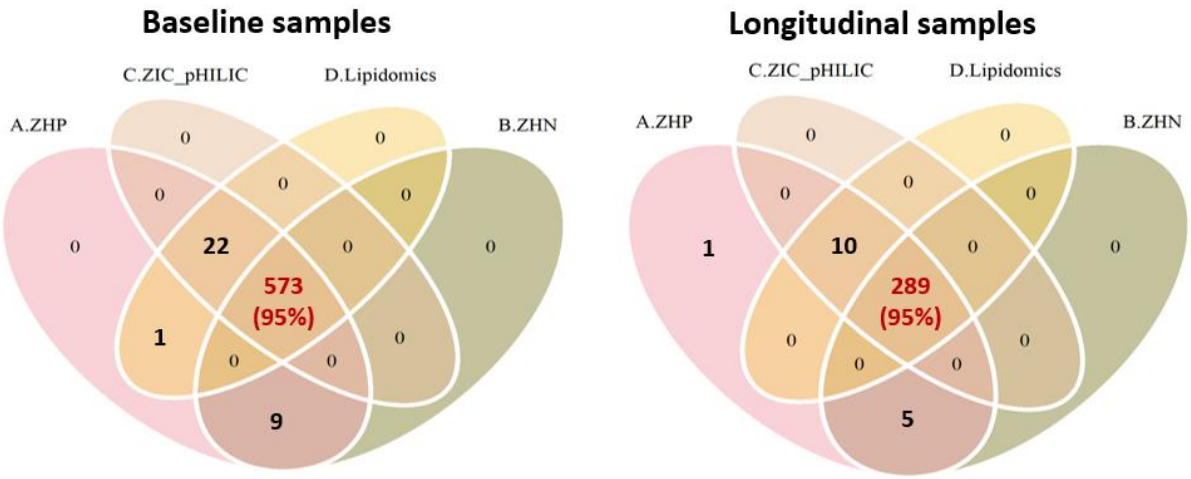

FIGURE E1. Overview of baseline and longitudinal samples available for four all-feature metabolomics datasets (Batch 1-17). Two urinary datasets (A.ZHP and B.ZHN) and two blood datasets (C.ZIC_pHILIC and D.Lipidomics) were included for sample selection. Due to the time limitation, urinary datasets with 573 adult baseline samples were used for further analysis. A.ZHP = urinary dataset from ZIC-HILIC positive method; B.ZHN = urinary dataset from ZIC-HILIC negative method.

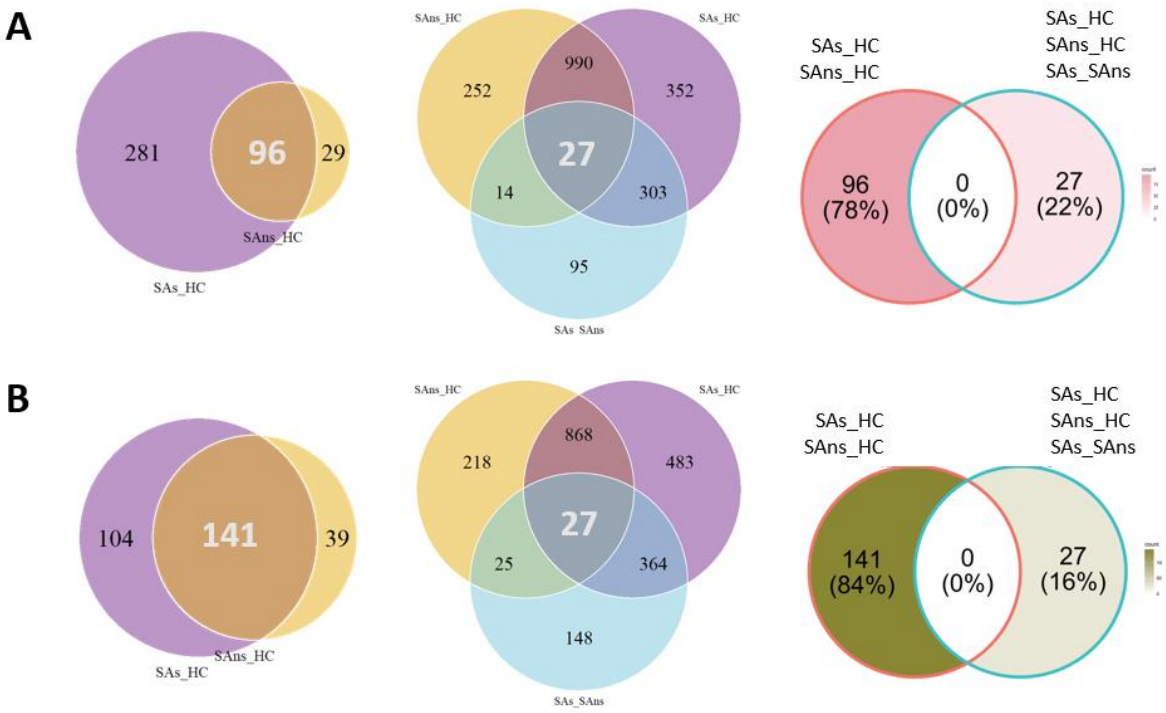

FIGURE E2. Venn diagram used for feature selection from **(A)** ZIC-HILIC positive dataset and **(B)** ZIC-HILIC negative dataset. From left to right, each Venn diagram demonstrates the comparison as follows: (i) the significant altered features ($p < 0.05$ in **(A)**/$p < 0.001$ in **(B)** and fold change > 2) in both SAns vs HC and SAs vs HC; (ii) the significant altered features ($p < 0.05$) in both SAns vs HC and SAs vs HC and SAns vs SAs; (iii) the sum up of selected features. HC = healthy controls; SAns = non-smokers with severe asthma; SAs = smokers or ex-smokers with severe asthma.

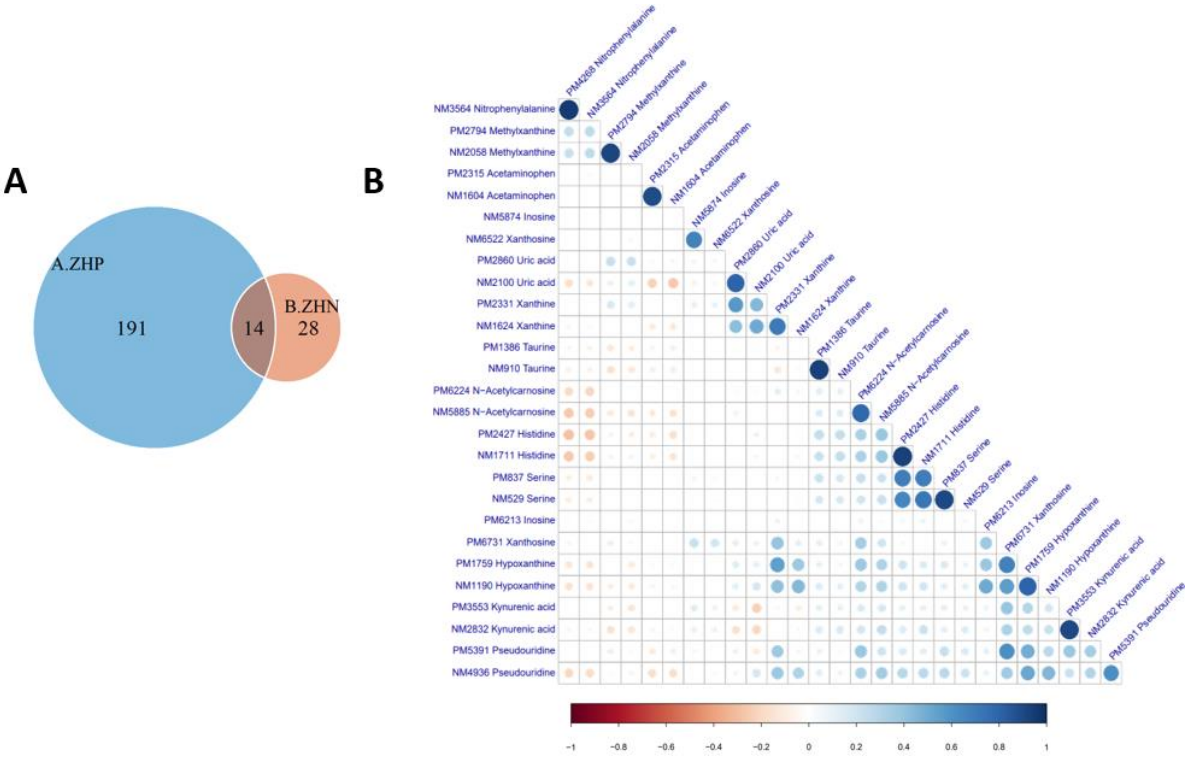

FIGURE E3. Metabolites identified from both ZHP and ZHN method. **(A)** Venn diagram illustrating the number of metabolites that were detected by two methods. **(B)** Correlation plot of these 14 overlapping metabolites, of which Inosine and Xanthosine show unexpected correlations. A.ZHP = dataset from ZIC-HILIC positive method; B.ZHN = dataset from ZIC-HILIC negative method.

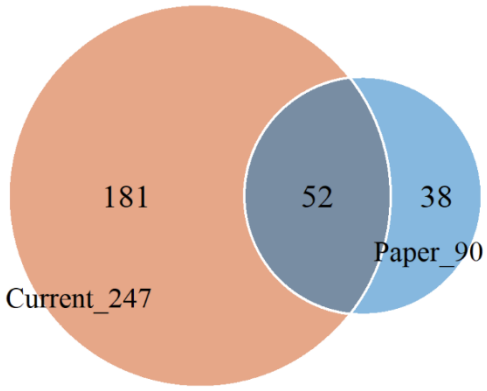

FIGURE E4. Venn diagram comparing the number of identified metabolites with previous version. Ninety metabolites were targeted pooled from in house library in 2016, and 247 metabolites are annotated in current library. For more information included for sub-phenotyping, 285 metabolites were included for further analysis.

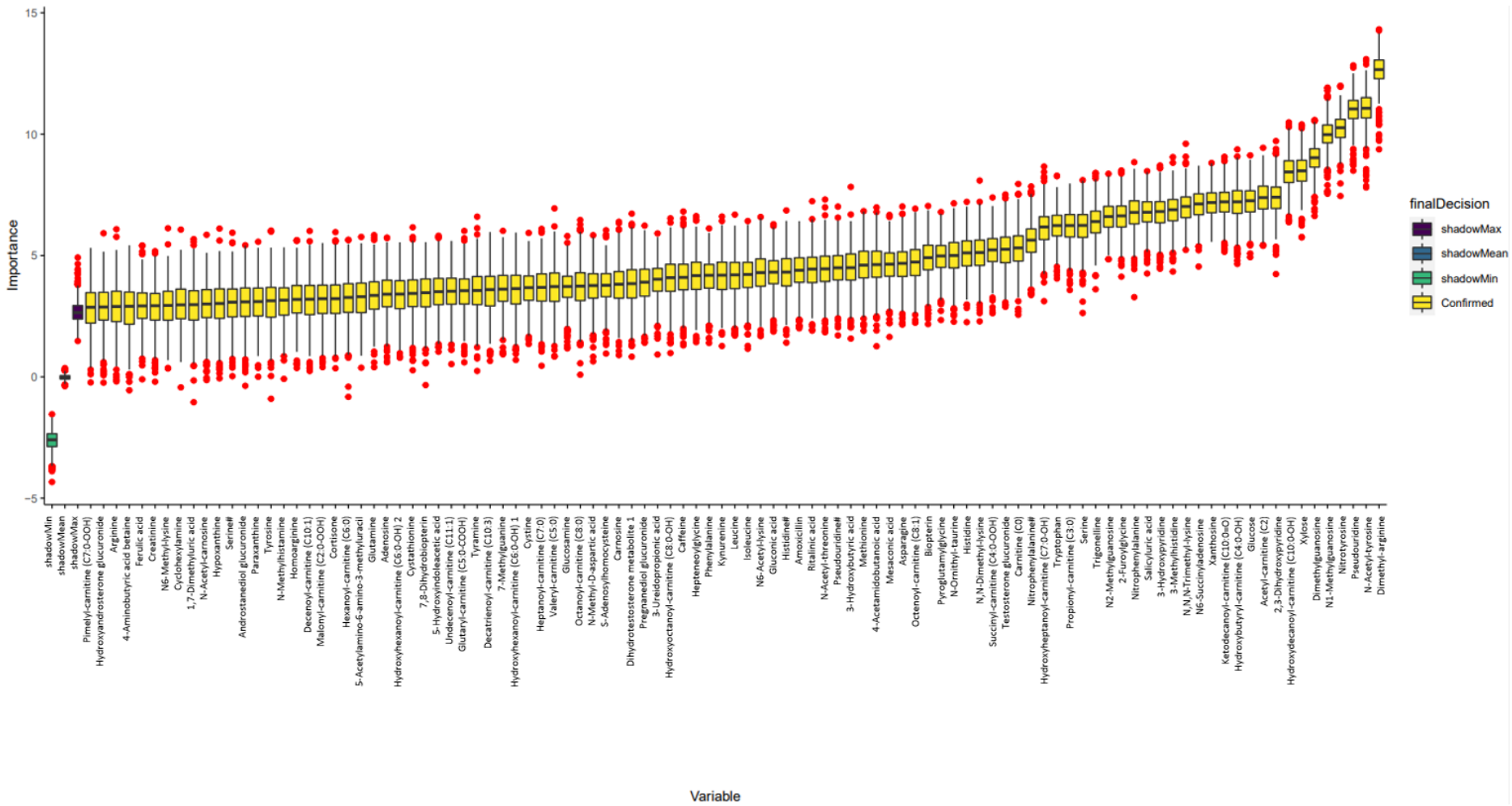

FIGURE E5. Importance of metabolites associated with classification of sub-groups. The Boruta algorithm identified all variables with significant importance for the classification of four clusters and furthermore defines each variable as confirmed (n=*101*, with increasing importance from left to right), tentatively important (n=*10*) or unimportant (n=*169*).

Overlapping metabolites detected by ZIC-HILIC negative ionization mode.

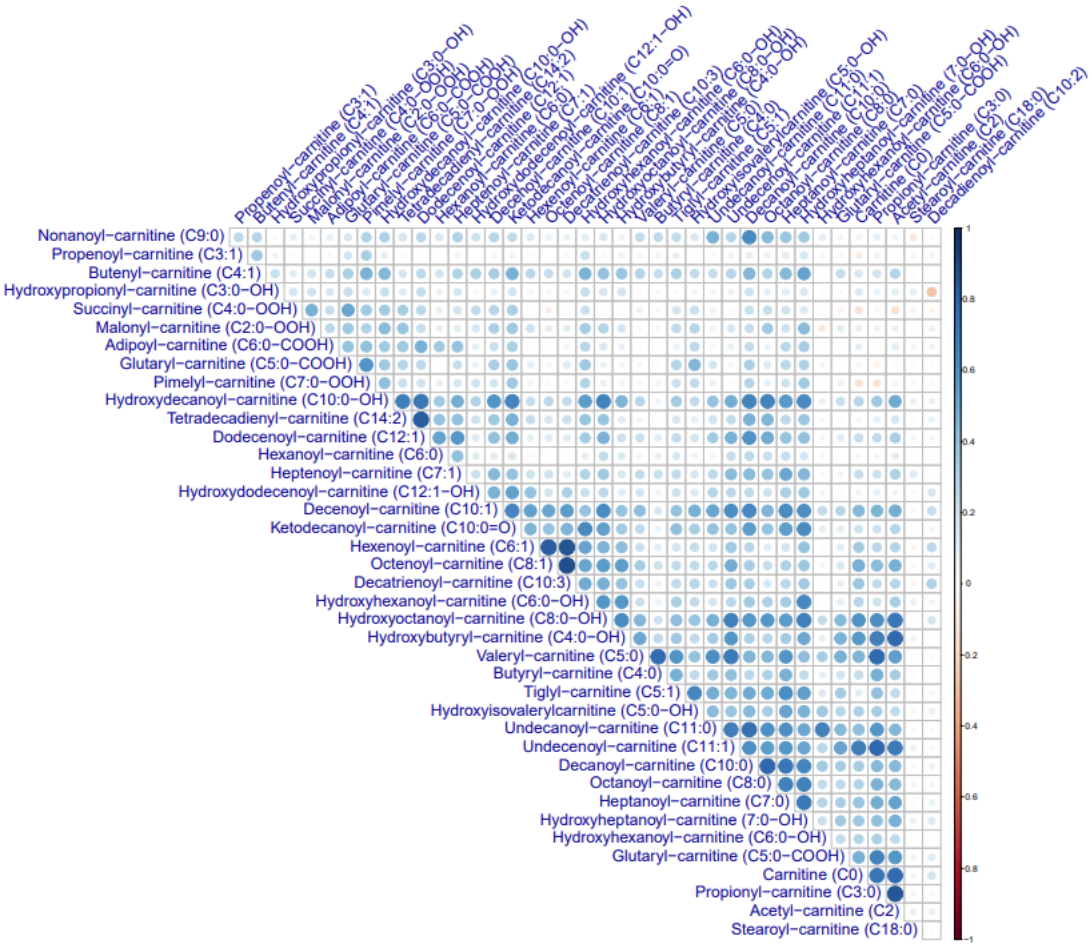

FIGURE E6. Correlation plot of 40 carnitine species from current in-house library using data from 478 asthmatics.

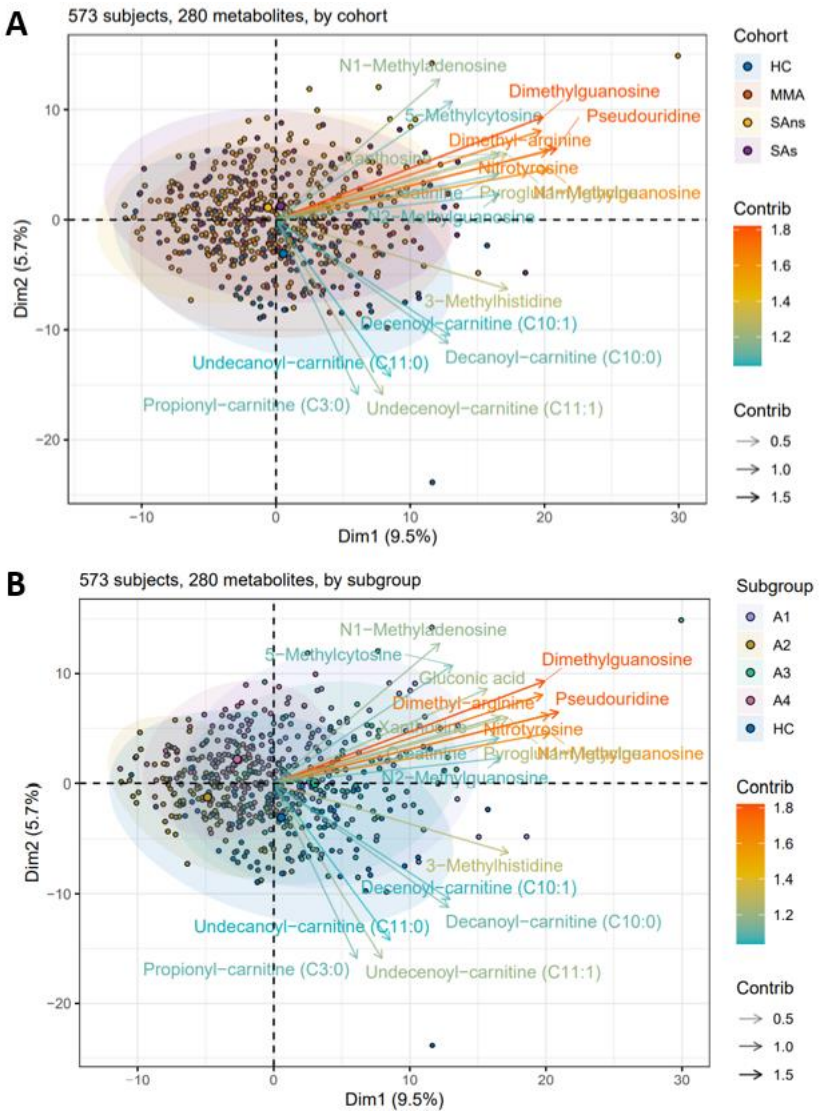

FIGURE E7. PCA plot of metabolites and individuals by **(A)** clinical cohort and **(B)** subtypes clustered by metabolites. All asthmatics and healthy participants from U-BIOPRED are plotted and colored according to their cohort or identified subtype. The relative magnitude and direction of 20 most contributing metabolites correlations with the PCs are shown with arrows and colored based on their contributions. HC = healthy non-smoking controls; MMA = noon-smokers with mild-to-moderate asthma; SAns = non-smokers with severe asthma; SAs = smokers or ex-smokers with severe asthma.

TABLE E1. Overview of four all-feature metabolomics datasets.

	Urine (Karolinska – Gunma)		Blood (UCSD)	
Datasets	**A.ZHP (ZIC-HILIC POS)**	**B. ZHN (ZIC-HILIC NEG)**	**C. ZIC-pHILIC POS**	**D. Lipidomics**
Baseline samples	605	582	595	596
Longitudinal samples	305	294	302	302
Samples	910	876	897	898
Features	15,583	16,934	6,907	14,770

TABLE E2. Information of 280 metabolites and statistical analysis by cohort.

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
1	ZHP	Erucamide	1 (0.66,1.52)	0.92 (0.7,1.35)	0.85 (0.62,1.35)	0.78 (0.57,1.16)	7.46E-01	1.88E-01	1.00E+00	9.23E-01	8.24E-01	UAUDZVJPLUQNMU-KTKRTIGZSA-N
2	ZHP	Sulfamethoxazole	1 (0.77,1.26)	0.95 (0.69,1.3)	1.15 (0.95,1.45)	1.13 (0.89,1.48)	2.40E-01	8.53E-02	9.95E-01	4.94E-01	6.62E-01	JLKIGFTWXXRPMT-UHFFFAOYSA-N
3	ZHP	Caffeine	1 (0.53,1.88)	0.56 (0.4,1.04)	0.92 (0.64,1.52)	1.02 (0.68,1.74)	2.02E-01	7.55E-02	2.08E-01	9.35E-01	9.96E-01	RYYVLZVUVIJVGH-UHFFFAOYSA-N
4	ZHP	N-Cinnamoylglycine	1 (0.8,1.27)	0.88 (0.64,1.09)	0.88 (0.68,1.14)	0.81 (0.61,1.08)	7.45E-01	1.88E-01	9.53E-01	9.25E-01	6.85E-01	YAADMLWHGMUGQL-VOTSOKGWSA-N
5	ZHP	Salicyluric acid	1 (0.76,1.28)	1.01 (0.75,1.28)	1.25 (1.01,1.46)	1.53 (1.16,2.16)	2.56E-02	1.35E-02	7.99E-01	7.91E-01	1.73E-01	ONJSZLXSECQROL-UHFFFAOYSA-N
6	ZHP	Hippuric acid	1 (0.88,1.16)	1.03 (0.86,1.18)	1.04 (0.91,1.12)	1.01 (0.88,1.09)	5.15E-01	1.47E-01	9.97E-01	9.95E-01	7.47E-01	QIAFMBKCNZACKA-UHFFFAOYSA-N
7	ZHP	Acetaminophen	1 (0.91,1.09)	1.07 (0.96,1.19)	1.19 (1.08,1.33)	1.16 (1.05,1.45)	2.80E-03	1.85E-03	6.26E-01	5.27E-03	1.15E-02	RZVAJINKPMORJF-UHFFFAOYSA-N
8	ZHP	2-Furoylglycine	1.02 (0.69,1.49)	0.83 (0.55,1.15)	1.03 (0.66,1.5)	1.18 (0.68,1.93)	1.62E-01	6.30E-02	4.10E-01	9.89E-01	9.04E-01	KSPQDMRTZZYQLM-UHFFFAOYSA-N
9	ZHP	Paraxanthine	1 (0.76,1.3)	0.89 (0.68,1.09)	0.98 (0.78,1.17)	1 (0.8,1.22)	1.70E-01	6.54E-02	1.18E-01	7.01E-01	8.06E-01	QUNWUDVFRNGTCO-UHFFFAOYSA-N
10	ZHP	3-Indoleacrylic acid	0.99 (0.73,1.31)	1.2 (0.9,1.53)	0.86 (0.69,1.11)	0.73 (0.55,0.97)	9.65E-05	9.25E-05	9.67E-01	1.66E-01	1.32E-03	PLVPPLCLBIEYEA-AATRIKPKSA-N
11	ZHP	3-Hydroxyanthranilic acid	1 (0.83,1.23)	0.9 (0.73,1.23)	1.02 (0.87,1.21)	0.87 (0.71,1.06)	2.28E-01	8.29E-02	9.59E-01	9.33E-01	7.02E-01	WJXSWCUQABXPFS-UHFFFAOYSA-N
12	ZHP	4-Acetamidobutanoic acid	1 (0.9,1.11)	1.05 (0.95,1.17)	1.1 (1.03,1.21)	1.07 (0.98,1.2)	2.60E-02	1.36E-02	4.57E-01	1.46E-02	1.54E-01	UZTFMUBKZQVKLK-UHFFFAOYSA-N
13	ZHP	Nicotinic acid	1 (0.65,1.5)	0.93 (0.62,1.39)	0.98 (0.74,1.41)	1.08 (0.76,1.52)	5.76E-01	1.56E-01	8.73E-01	9.94E-01	9.32E-01	PVNIIMVLHYAWGP-UHFFFAOYSA-N
14	ZHP	Pantothenol	1 (0.64,1.55)	0.99 (0.68,1.44)	0.97 (0.69,1.29)	1.01 (0.68,1.42)	9.84E-01	2.34E-01	9.90E-01	9.81E-01	9.96E-01	SNPLKNRPJHDVJA-ZETCQYMHSA-N
15	ZHP	Ferulic acid	1 (0.78,1.32)	0.95 (0.72,1.34)	0.99 (0.79,1.28)	1.14 (0.91,1.46)	9.30E-01	2.25E-01	9.45E-01	9.87E-01	1.00E+00	KSEBMYQBYZTDHS-HWKANZROSA-N
16	ZHP	Pantothenic acid	1.01 (0.83,1.21)	1.1 (0.87,1.34)	1.01 (0.86,1.18)	0.92 (0.74,1.23)	3.08E-01	1.03E-01	7.22E-01	1.00E+00	8.25E-01	GHOKWGTUZJEAQD-ZETCQYMHSA-N
17	ZHP	N-Methylnicotinamide	1 (0.81,1.24)	0.97 (0.83,1.17)	0.98 (0.86,1.2)	1.07 (0.91,1.31)	3.09E-01	1.02E-01	9.78E-01	9.94E-01	5.01E-01	ZYVXHFWBYUDDBM-UHFFFAOYSA-N
18	ZHP	Phenylacetylglutamine	1 (0.92,1.09)	1.04 (0.95,1.13)	1.04 (0.96,1.11)	1.05 (0.97,1.14)	9.97E-02	4.20E-02	7.20E-01	4.55E-01	6.09E-02	JFLIEFSWGNOPJJ-JTQLQIEISA-N
19	ZHP	Octenoyl-carnitine (C8:1)	1 (0.75,1.34)	0.89 (0.68,1.21)	0.66 (0.52,0.92)	0.64 (0.45,1.04)	2.28E-05	2.51E-05	9.85E-01	2.27E-04	3.59E-02	LOSHAHDSFZXVCT-LXKVQUBZSA-N
20	ZHP	Methylxanthine	1 (0.74,1.33)	0.74 (0.57,0.99)	0.94 (0.8,1.24)	1.03 (0.85,1.39)	3.50E-02	1.78E-02	2.90E-01	9.99E-01	6.45E-01	MVOYJPOZRLFTCP-UHFFFAOYSA-N

Idx	Method	Metabolites	Fold Change				KW p-value	FDR	Post hoc pairwise comparison			INCHIKEY
			HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)			MMA_HC	SAns_HC	SAs_HC	
21	ZHP	N1-Methyl-4-pyridone-3-carboxamide	1 (0.88,1.13)	1.07 (0.94,1.2)	1.02 (0.91,1.11)	1.09 (0.91,1.19)	7.31E-01	1.86E-01	6.97E-01	9.80E-01	9.87E-01	KTLRWTOPTKGYQY-UHFFFAOYSA-N
22	ZHP	Valeryl-carnitine (C5:0)	1 (0.84,1.19)	0.81 (0.68,1.01)	0.64 (0.56,0.75)	0.67 (0.57,0.86)	4.20E-09	9.58E-09	1.23E-01	3.62E-09	5.35E-04	VSNFQQXVMPSASB-SNVBAGLBSA-N
23	ZHP	Nicotinamide	1 (0.82,1.26)	1.04 (0.88,1.25)	0.87 (0.75,1.01)	0.85 (0.7,1.01)	4.73E-03	3.01E-03	9.13E-01	1.26E-01	1.41E-01	DFPAKSUCGFBDDF-UHFFFAOYSA-N
24	ZHP	Butyryl-carnitine (C4:0)	1 (0.85,1.18)	0.91 (0.78,1.08)	0.75 (0.64,0.84)	0.86 (0.73,0.97)	6.23E-06	7.63E-06	7.55E-01	1.71E-05	5.62E-02	QWYFHHGCZUCMBN-SECBINFHSA-N
25	ZHP	1,3-Dimethyluric acid	0.99 (0.78,1.25)	0.72 (0.55,0.98)	1.25 (1,1.58)	1.64 (1.29,2.04)	2.98E-08	5.80E-08	2.82E-01	6.47E-02	4.61E-04	OTSBKHHWSQYEHK-UHFFFAOYSA-N
26	ZHP	Kynurenic acid	1 (0.89,1.12)	1.09 (0.93,1.21)	0.9 (0.81,0.99)	0.96 (0.85,1.07)	1.88E-03	1.34E-03	6.24E-01	1.15E-01	7.26E-01	HCZHHEIFKROPDY-UHFFFAOYSA-N
27	ZHP	Propionyl-carnitine (C3:0)	0.99 (0.74,1.34)	0.61 (0.42,0.97)	0.39 (0.26,0.55)	0.42 (0.29,0.6)	5.89E-10	1.56E-09	7.26E-02	4.10E-10	4.08E-04	UFAHZIUFPNSHSL-MRVPVSSYSA-N
28	ZHP	5-Hydroxyindoleacetic acid	1 (0.93,1.07)	1.11 (0.98,1.2)	1.11 (1.03,1.19)	1.14 (1.05,1.27)	7.74E-03	4.74E-03	2.60E-01	1.21E-02	9.28E-03	DUUGKQCEGZLZNO-UHFFFAOYSA-N
29	ZHP	1,7-Dimethyluric acid	0.99 (0.71,1.36)	0.68 (0.52,0.99)	1.08 (0.92,1.53)	1.3 (1.06,1.74)	8.87E-04	6.90E-04	2.61E-01	7.14E-01	1.57E-01	NOFNCLGCUJJPKU-UHFFFAOYSA-N
30	ZHP	N-Acetyl-glutamic acid	1 (0.88,1.13)	1.09 (0.97,1.22)	1.12 (1,1.22)	1.09 (0.96,1.21)	9.21E-02	3.93E-02	2.42E-01	6.27E-02	2.85E-01	RFMMMVDNIPUKGG-YFKPBYRVSA-N
31	ZHP	Nicotinuric acid	1 (0.82,1.19)	0.97 (0.8,1.18)	1.27 (1.12,1.5)	1.64 (1.31,2.16)	1.14E-10	3.77E-10	9.92E-01	1.35E-04	1.57E-08	ZBSGKPYXQINNGF-UHFFFAOYSA-N
32	ZHP	Indoxyl-sulfate	1 (0.78,1.27)	1.02 (0.81,1.31)	1.06 (0.87,1.23)	1.11 (0.9,1.34)	4.55E-01	1.34E-01	8.60E-01	9.57E-01	4.44E-01	BXFFHSIDQOFMLE-UHFFFAOYSA-N
33	ZHP	4-Pyridoxic acid	1 (0.89,1.15)	1.02 (0.86,1.16)	1.03 (0.89,1.14)	1.15 (0.88,1.39)	9.17E-01	2.22E-01	1.00E+00	9.69E-01	9.99E-01	HXACOUQIXZGNBF-UHFFFAOYSA-N
34	ZHP	N-Acetyl-glutamine	1 (0.79,1.27)	1.06 (0.83,1.45)	1.06 (0.85,1.23)	1.04 (0.83,1.22)	9.64E-01	2.31E-01	9.56E-01	9.76E-01	9.89E-01	KSMRODHGGIIXDV-YFKPBYRVSA-N
35	ZHP	N-Acetyl-asparagine	1 (0.83,1.17)	1.07 (0.91,1.37)	1.07 (0.88,1.23)	1.09 (0.92,1.28)	8.56E-01	2.12E-01	8.40E-01	9.88E-01	9.65E-01	HXFOXFJUNFFYMO-BYPYZUCNSA-N
36	ZHP	Xanthine	1 (0.87,1.14)	1.22 (1.01,1.39)	1.12 (0.97,1.3)	1.03 (0.87,1.29)	1.71E-01	6.50E-02	2.78E-01	1.50E-01	6.54E-01	LRFVTYWOQMYALW-UHFFFAOYSA-N
37	ZHP	2,3-Dihydroxypyridine	1 (0.42,2.39)	0.7 (0.35,1.31)	1.19 (0.6,2.24)	2.36 (1.06,4.93)	1.22E-03	9.38E-04	5.87E-01	9.60E-01	3.92E-02	GGOZGYRTNQBSSA-UHFFFAOYSA-N
38	ZHP	Acetyl-carnitine (C2)	1 (0.83,1.2)	0.67 (0.5,0.97)	0.43 (0.35,0.53)	0.54 (0.37,0.85)	1.54E-08	3.09E-08	1.11E-01	9.51E-09	2.70E-03	RDHQFKQIGNGIED-MRVPVSSYSA-N
39	ZHP	Hypoxanthine	1 (0.84,1.17)	1.19 (0.98,1.43)	0.98 (0.83,1.11)	0.97 (0.77,1.2)	2.85E-02	1.47E-02	3.85E-01	7.78E-01	7.80E-01	FDGQSTZJBFJUBT-UHFFFAOYSA-N
40	ZHP	2-Deoxyinosine	1 (0.67,1.39)	0.81 (0.63,1.13)	0.94 (0.73,1.27)	1.08 (0.77,1.57)	3.59E-01	1.14E-01	6.97E-01	1.00E+00	8.98E-01	VGONTNSXDCQUGY-RRKCRQDMSA-N
41	ZHP	1-Methyluric acid	1 (0.68,1.49)	0.7 (0.51,1.02)	1.24 (0.94,1.7)	1.75 (1.25,2.53)	4.47E-10	1.23E-09	1.11E-01	2.39E-01	6.03E-05	QFDRTQONISXGJA-UHFFFAOYSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
42	ZHP	Acetyl-citrulline	1 (0.8,1.27)	1.1 (0.9,1.45)	1.1 (0.95,1.38)	1.28 (1.06,1.62)	4.05E-02	1.98E-02	8.91E-01	4.81E-01	2.80E-02	WMQMIOYQXNRROC-LURJTMIESA-N
43	ZHP	Dimethylguanosine	1 (0.9,1.14)	1.14 (0.99,1.31)	1.15 (1.05,1.27)	1.18 (1.06,1.33)	1.47E-03	1.09E-03	1.12E-01	6.44E-03	9.90E-04	RSPURTUNRHNVGF-IOSLPCCCSA-N
44	ZHP	7-Methyluric acid	1 (0.73,1.4)	0.9 (0.67,1.26)	1.2 (0.92,1.58)	1.13 (0.84,1.52)	3.67E-01	1.15E-01	1.00E+00	5.09E-01	8.68E-01	YHNNPKUFPWLTOP-UHFFFAOYSA-N
45	ZHP	Ritalinic acid	1 (0.79,1.27)	1.13 (0.95,1.4)	1.02 (0.88,1.25)	1.03 (0.87,1.28)	5.14E-01	1.47E-01	5.51E-01	9.76E-01	8.01E-01	INGSNVSERUZOAK-UHFFFAOYSA-N
46	ZHP	5-S-Methylthioadenosine	1 (0.72,1.3)	0.94 (0.73,1.33)	1.18 (0.96,1.55)	1.07 (0.91,1.45)	3.98E-02	1.98E-02	9.60E-01	2.00E-01	9.23E-01	WUUGFSXJNOTRMR-IOSLPCCCSA-N
47	ZHP	Acetaminophen glucuronide	1 (0.74,1.34)	1.04 (0.74,1.42)	1.47 (1.03,1.8)	1.56 (0.99,2.62)	9.96E-03	5.94E-03	9.37E-01	6.41E-02	1.87E-02	IPROLSVTVHAQLE-BYNIDDHOSA-N
48	ZHP	N6-Succinyladenosine	1 (0.9,1.13)	1.04 (0.94,1.17)	1.04 (0.96,1.14)	1.08 (0.98,1.22)	7.37E-02	3.29E-02	3.76E-01	2.52E-01	4.54E-02	VKGZCEJTCKHMRL-MDBUBQOGSA-N
49	ZHP	N1-Methylguanosine	1 (0.89,1.12)	1.03 (0.93,1.15)	0.97 (0.87,1.08)	1.02 (0.9,1.15)	1.71E-01	6.46E-02	6.90E-01	9.86E-01	6.38E-01	UTAIYTHAJQNQDW-KQYNXXCUSA-N
50	ZHP	Tryptophan betaine	1 (0.59,1.66)	0.89 (0.52,1.61)	0.69 (0.43,0.97)	0.52 (0.31,1.22)	6.39E-02	2.91E-02	9.61E-01	2.10E-01	8.26E-02	AOHCBEAZXHZMOR-ZDUSSCGKSA-N
51	ZHP	Inosine	1 (0.8,1.23)	1.42 (1.1,1.79)	1.52 (1.28,1.84)	1.8 (1.45,2.18)	2.13E-03	1.45E-03	8.69E-02	5.41E-03	1.97E-03	UGQMRVRMYYASKQ-KQYNXXCUSA-N
52	ZHP	Cyclohexylamine	1 (0.94,1.06)	0.98 (0.93,1.02)	0.98 (0.92,1.01)	1.01 (0.96,1.06)	7.80E-02	3.42E-02	5.71E-01	4.36E-01	9.37E-01	PAFZNILMFXTMIY-UHFFFAOYSA-N
53	ZHP	N2-Methylguanosine	1 (0.88,1.12)	1.04 (0.91,1.22)	1 (0.89,1.1)	1.03 (0.88,1.16)	5.27E-01	1.48E-01	6.04E-01	1.00E+00	9.73E-01	SLEHROROQDYRAW-KQYNXXCUSA-N
54	ZHP	Pseudouridine	1 (0.92,1.09)	1.07 (0.97,1.18)	1.03 (0.96,1.1)	1.03 (0.94,1.1)	2.81E-01	9.73E-02	2.31E-01	4.61E-01	5.58E-01	PTJWIQPHWPFNBW-GBNDHIKLSA-N
55	ZHP	N-Acetyl-D-galactosamine	1 (0.9,1.1)	1.06 (0.96,1.16)	1.09 (1.01,1.19)	1.12 (1,1.24)	2.77E-02	1.44E-02	3.58E-01	4.12E-02	2.77E-02	OVRNDRQMDRJTHS-KEWYIRBNSA-N
56	ZHP	Uric acid	1 (0.93,1.07)	1.01 (0.95,1.08)	0.99 (0.96,1.07)	0.97 (0.92,1.04)	8.65E-01	2.13E-01	9.67E-01	9.18E-01	1.00E+00	LEHOTFFKMJEONL-UHFFFAOYSA-N
57	ZHP	Phenylalanine	1 (0.87,1.15)	1.12 (0.97,1.29)	1.02 (0.9,1.13)	1.01 (0.89,1.17)	2.53E-01	8.85E-02	2.96E-01	9.56E-01	1.00E+00	COLNVLDHVKWLRT-QMMMGPOBSA-N
58	ZHP	Kynurenine	1 (0.77,1.27)	1.02 (0.83,1.38)	1.14 (0.92,1.43)	1.26 (0.95,1.54)	3.85E-01	1.19E-01	9.26E-01	4.00E-01	4.81E-01	YGPSJZOEDVAXAB-QMMMGPOBSA-N
59	ZHP	Homarine	1 (0.49,2.17)	1.2 (0.56,1.9)	1.01 (0.56,1.53)	1.09 (0.58,1.74)	5.89E-01	1.58E-01	5.81E-01	9.38E-01	7.91E-01	BRTLKRNVNFIOPJ-UHFFFAOYSA-N
60	ZHP	2-Methylpyrrolidine	1 (0.77,1.24)	1.39 (0.99,2.06)	1.11 (0.91,1.41)	1.09 (0.76,1.4)	3.38E-01	1.10E-01	3.23E-01	8.31E-01	9.95E-01	RGHPCLZJAFCTIK-UHFFFAOYSA-N
61	ZHP	Amoxicillin	1.01 (0.63,1.61)	0.84 (0.6,1.39)	0.96 (0.71,1.53)	1.19 (0.8,2.18)	1.70E-01	6.50E-02	9.82E-01	7.39E-01	3.41E-01	LSQZJLSUYDQPKJ-NJBDSQKTSA-N
62	ZHP	Tryptophan	1 (0.81,1.21)	1.11 (0.9,1.38)	1.05 (0.89,1.24)	1.12 (0.83,1.4)	7.55E-01	1.89E-01	7.00E-01	9.45E-01	9.45E-01	QIVBCDIJIAJPQS-VIFPVBQESA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
63	ZHP	Adenosine	1 (0.87,1.16)	1.07 (0.89,1.27)	1.1 (0.96,1.28)	1.2 (0.98,1.4)	5.50E-01	1.54E-01	8.97E-01	5.82E-01	5.50E-01	OIRDTQYFTABQOQ-KQYNXXCUSA-N
64	ZHP	N-Acetylneuraminic acid	1 (0.89,1.12)	1.14 (1.03,1.25)	1.11 (1,1.22)	1.26 (1.11,1.39)	5.65E-05	5.93E-05	1.01E-01	3.87E-03	1.76E-05	SQVRNKJHWKZAKO-PFQGKNLYSA-N
65	ZHP	7,8-Dihydrobiopterin	1 (0.86,1.18)	1.09 (0.91,1.27)	0.97 (0.84,1.11)	1.06 (0.89,1.21)	4.70E-01	1.36E-01	8.59E-01	9.72E-01	9.52E-01	FEMXZDUTFRTWPE-AWFVSMACSA-N
66	ZHP	Tyramine	1 (0.85,1.18)	0.98 (0.86,1.18)	0.88 (0.77,1.03)	0.82 (0.71,0.96)	4.84E-03	3.05E-03	1.00E+00	3.70E-02	5.42E-02	DZGWFCGJZKJUFP-UHFFFAOYSA-N
67	ZHP	7-Methylguanine	1 (0.88,1.14)	0.98 (0.86,1.12)	0.92 (0.85,1.06)	0.91 (0.83,1.1)	6.06E-01	1.60E-01	9.88E-01	8.25E-01	9.87E-01	FZWGECJQACGGTI-UHFFFAOYSA-N
68	ZHP	Proline betaine	1 (0.64,1.61)	0.84 (0.56,1.19)	0.81 (0.54,1.11)	0.46 (0.29,0.78)	2.11E-03	1.45E-03	9.63E-01	1.81E-01	2.36E-03	CMUNUTVVOOHQPW-LURJTMIESA-N
69	ZHP	Guanine	1 (0.74,1.39)	1.28 (0.99,1.65)	0.96 (0.76,1.27)	0.81 (0.61,1.06)	7.89E-03	4.74E-03	3.23E-01	9.15E-01	3.36E-01	UYTPUPDQBNUYGX-UHFFFAOYSA-N
70	ZHP	Trigonelline	1 (0.72,1.36)	1 (0.72,1.28)	1.46 (1.13,1.77)	1.65 (1.14,2.18)	2.87E-04	2.47E-04	9.43E-01	3.98E-02	1.80E-02	WWNNZCOKKKDOPX-UHFFFAOYSA-N
71	ZHP	N-Methyl-proline	1 (0.66,1.57)	0.67 (0.42,1.08)	0.8 (0.53,1.08)	0.71 (0.46,1.12)	1.28E-01	5.13E-02	1.86E-01	1.48E-01	2.24E-01	CWLQUGTUXBXTLF-YFKPBYRVSA-N
72	ZHP	Betaine	1 (0.84,1.2)	0.98 (0.85,1.14)	0.9 (0.79,1.01)	0.93 (0.78,1.11)	3.13E-01	1.03E-01	7.16E-01	2.35E-01	6.71E-01	KWIUHFFTVRNATP-UHFFFAOYSA-N
73	ZHP	Tyrosine	1 (0.82,1.27)	1.12 (0.93,1.34)	1.09 (0.92,1.28)	1.06 (0.87,1.28)	2.96E-01	1.00E-01	5.81E-01	4.79E-01	1.00E+00	OUYCCCASQSFEME-QMMMGPOBSA-N
74	ZHP	Theanine	1 (0.5,1.83)	1.48 (0.67,5.01)	1.38 (0.73,2.06)	0.91 (0.5,1.56)	5.26E-01	1.49E-01	5.39E-01	8.04E-01	9.97E-01	DATAGRPVKZEWHA-YFKPBYRVSA-N
75	ZHP	4-Guanidinobutanoic acid	1 (0.74,1.29)	0.8 (0.61,1.06)	0.79 (0.67,1.03)	0.73 (0.6,0.97)	8.87E-02	3.86E-02	7.51E-01	1.19E-01	1.11E-01	TUHVEAJXIMEOSA-UHFFFAOYSA-N
76	ZHP	Proline	1 (0.87,1.13)	1.01 (0.89,1.14)	1.09 (0.97,1.19)	1.07 (0.9,1.24)	2.87E-01	9.84E-02	9.93E-01	5.51E-01	7.31E-01	ONIBWKKTOPOVIA-BYPYZUCNSA-N
77	ZHP	Dimethylglycine	1 (0.73,1.39)	0.92 (0.74,1.24)	0.9 (0.75,1.2)	0.97 (0.76,1.29)	6.66E-01	1.74E-01	9.75E-01	9.78E-01	9.30E-01	FFDGPVCHZBVARC-UHFFFAOYSA-N
78	ZHP	Choline	1 (0.83,1.19)	1.17 (0.99,1.34)	1.2 (1.04,1.35)	1.13 (0.97,1.28)	2.14E-02	1.17E-02	1.43E-01	1.33E-02	4.50E-01	OEYIOHPDSNJKLS-UHFFFAOYSA-N
79	ZHP	Taurine	1 (0.73,1.43)	0.96 (0.61,1.33)	0.85 (0.66,1.18)	0.88 (0.55,1.4)	6.52E-01	1.71E-01	1.00E+00	8.33E-01	1.00E+00	XOAAWQZATWQOTB-UHFFFAOYSA-N
80	ZHP	Carnitine (C0)	1 (0.89,1.15)	0.88 (0.75,1.04)	0.68 (0.59,0.75)	0.76 (0.63,0.96)	1.10E-06	1.52E-06	3.89E-01	1.41E-06	5.67E-02	PHIQHXFUZVPYII-ZCFIWIBFSA-N
81	ZHP	4-Imidazoleacetic acid	1 (0.85,1.16)	1 (0.87,1.15)	1.01 (0.91,1.18)	0.98 (0.84,1.17)	9.84E-01	2.33E-01	9.97E-01	9.93E-01	1.00E+00	PRJKNHOMHKJCEJ-UHFFFAOYSA-N
82	ZHP	Creatine	1.01 (0.73,1.46)	1.11 (0.82,1.52)	1.43 (1.1,1.91)	1.21 (0.96,1.61)	3.48E-03	2.23E-03	8.16E-01	4.25E-03	9.14E-02	CVSVTCORWBXHQV-UHFFFAOYSA-N
83	ZHP	N-Acetyl-histamine	1 (0.73,1.38)	1.19 (0.97,1.84)	1.27 (1.03,1.73)	1.72 (1.36,2.53)	9.86E-05	9.32E-05	1.25E-01	6.33E-03	3.07E-05	XJWPISBUKWZALE-UHFFFAOYSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
84	ZHP	2-Aminoadipic acid	1 (0.82,1.2)	0.93 (0.83,1.15)	0.92 (0.83,1.12)	0.91 (0.8,1.1)	5.51E-01	1.54E-01	7.38E-01	4.88E-01	6.97E-01	OYIFNHCXNCRBQI-BYPYZUCNSA-N
85	ZHP	N6-Acetyl-lysine	1 (0.92,1.09)	0.96 (0.88,1.07)	0.91 (0.83,0.99)	0.89 (0.81,0.99)	1.55E-01	6.07E-02	8.64E-01	2.24E-01	1.76E-01	DTERQYGMUDWYAZ-ZETCQYMHSA-N
86	ZHP	Creatinine	1 (0.98,1.03)	1.01 (0.98,1.04)	1 (0.98,1.02)	1.01 (0.98,1.03)	5.57E-01	1.53E-01	9.80E-01	8.97E-01	9.91E-01	DDRJAANPRJIHGJ-UHFFFAOYSA-N
87	ZHP	N2-Acetyl-histidine	1 (0.89,1.13)	1.1 (0.95,1.26)	1.02 (0.94,1.14)	1.03 (0.92,1.18)	3.37E-01	1.10E-01	3.17E-01	9.56E-01	8.80E-01	KBOJOGQFRVVWBH-ZETCQYMHSA-N
88	ZHP	Glutamate	1 (0.9,1.11)	1.14 (0.96,1.27)	1.14 (1.02,1.27)	1.18 (1.04,1.27)	1.20E-02	6.96E-03	4.17E-01	1.05E-02	3.35E-02	WHUUTDBJXJRKMK-VKHMYHEASA-N
89	ZHP	N-Acetyl-arginine	0.99 (0.86,1.17)	1.08 (0.94,1.26)	1.12 (0.99,1.28)	1.16 (1.03,1.31)	4.95E-02	2.29E-02	7.66E-01	1.25E-01	4.60E-02	SNEIUMQYRCDYCH-LURJTMIESA-N
90	ZHP	1-Methylnicotinamide	1 (0.85,1.18)	1.14 (0.97,1.3)	0.97 (0.84,1.09)	1.03 (0.83,1.21)	1.49E-02	8.42E-03	2.73E-01	6.97E-01	9.90E-01	LDHMAVIPBRSVRG-UHFFFAOYSA-O
91	ZHP	Proline-Hydroxyproline	1 (0.81,1.22)	1.01 (0.82,1.25)	0.93 (0.77,1.11)	1.01 (0.82,1.2)	3.96E-01	1.21E-01	8.80E-01	3.28E-01	7.39E-01	ONPXCLZMBSJLSP-CSMHCCOUSA-N
92	ZHP	N-Acetylcarnosine	1 (0.78,1.25)	0.94 (0.79,1.13)	0.76 (0.66,0.89)	0.73 (0.6,0.93)	1.40E-05	1.65E-05	7.24E-01	7.27E-05	1.77E-03	BKAYIFDRRZZKNF-SECBINFHSA-N
93	ZHP	N2-Acetyl-lysine	1 (0.74,1.34)	1.16 (0.91,1.41)	1.22 (0.93,1.46)	1.41 (1.1,1.67)	3.13E-03	2.05E-03	6.84E-01	5.86E-02	2.03E-03	VEYYWZRYIYDQJM-ZETCQYMHSA-N
94	ZHP	Glycocyamine	1 (0.9,1.11)	1.05 (0.85,1.2)	1.01 (0.91,1.12)	0.88 (0.76,1)	5.56E-01	1.53E-01	9.98E-01	9.99E-01	7.18E-01	BPMFZUMJYQTVII-UHFFFAOYSA-N
95	ZHP	N-Acetylputrescine	1 (0.84,1.21)	1.2 (0.97,1.43)	1.14 (1,1.31)	1.19 (1.01,1.4)	2.30E-02	1.23E-02	2.77E-01	7.77E-02	1.37E-02	KLZGKIDSEJWEDW-UHFFFAOYSA-N
96	ZHP	Glutamine	1 (0.89,1.12)	0.97 (0.86,1.1)	0.9 (0.82,1.01)	0.88 (0.78,1)	2.27E-02	1.23E-02	9.90E-01	1.51E-01	4.36E-02	ZDXPYRJPNDTMRX-VKHMYHEASA-N
97	ZHP	Homocitrulline	1 (0.85,1.17)	1.19 (0.98,1.3)	1.05 (0.89,1.17)	0.94 (0.8,1.1)	1.18E-01	4.79E-02	8.33E-01	9.70E-01	4.03E-01	XIGSAGMEBXLVJJ-YFKPBYRVSA-N
98	ZHP	Cytosine	1.01 (0.76,1.31)	0.87 (0.66,1.03)	0.96 (0.73,1.09)	1.02 (0.77,1.31)	1.32E-01	5.23E-02	1.53E-01	7.64E-01	1.00E+00	OPTASPLRGRRNAP-UHFFFAOYSA-N
99	ZHP	beta-Alanine	1 (0.94,1.06)	0.98 (0.94,1.02)	0.99 (0.94,1.03)	0.96 (0.92,1.01)	2.33E-01	8.42E-02	5.04E-01	6.21E-01	1.90E-01	UCMIRNVEIXFBKS-UHFFFAOYSA-N
100	ZHP	Serine	1 (0.9,1.13)	0.95 (0.84,1.1)	0.82 (0.75,0.92)	0.78 (0.71,0.89)	1.10E-06	1.48E-06	8.12E-01	6.97E-05	6.57E-05	MTCFGRXMJLQNBG-REOHCLBHSA-N
101	ZHP	Triethanolamine	1 (0.66,1.48)	1.01 (0.66,1.29)	1.08 (0.78,1.33)	0.99 (0.67,1.31)	5.53E-01	1.53E-01	9.90E-01	7.29E-01	9.99E-01	GSEJCLTVZPLZKY-UHFFFAOYSA-N
102	ZHP	Citrulline	1 (0.89,1.09)	1 (0.91,1.11)	1 (0.91,1.09)	0.98 (0.89,1.12)	9.94E-01	2.35E-01	1.00E+00	1.00E+00	9.96E-01	RHGKLRLOHDJJDR-BYPYZUCNSA-N
103	ZHP	Nicotine	1 (0.56,1.87)	0.98 (0.58,1.81)	0.91 (0.6,1.46)	2.73 (1.34,4.84)	4.49E-08	8.49E-08	9.52E-01	9.37E-01	1.28E-04	SNICXCGAKADSCV-UHFFFAOYSA-N
104	ZHP	Cystine	1 (0.86,1.17)	0.94 (0.84,1.07)	1.07 (0.96,1.23)	1.14 (0.99,1.35)	2.36E-03	1.58E-03	8.13E-01	2.65E-01	5.87E-02	LEVWYRKDKASIDU-IMJSIDKUSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
105	ZHP	Cystathionine	1 (0.77,1.32)	0.77 (0.61,1.07)	0.93 (0.81,1.2)	1.01 (0.83,1.34)	2.44E-01	8.63E-02	5.86E-01	1.00E+00	8.69E-01	ILRYLPWNYFXEMH-WHFBIAKZSA-N
106	ZHP	Glucosamine	1 (0.87,1.16)	1.08 (0.93,1.25)	0.93 (0.86,1.07)	1 (0.92,1.19)	7.12E-02	3.20E-02	5.93E-01	8.72E-01	8.00E-01	MSWZFWKMSRAUBD-IVMDWMLBSA-N
107	ZHP	Arginine	1 (0.83,1.2)	1.03 (0.87,1.21)	0.99 (0.86,1.14)	1.11 (0.89,1.32)	5.51E-01	1.53E-01	9.92E-01	9.97E-01	7.56E-01	ODKSFYDXXFIFQN-BYPYZUCNSA-N
108	ZHP	Dimethyl-arginine	1 (0.88,1.14)	1.07 (0.94,1.23)	1.07 (0.95,1.16)	1.08 (0.96,1.19)	5.80E-01	1.57E-01	6.81E-01	8.14E-01	5.77E-01	YDGMGEXADBMOMJ-LURJTMIESA-N
109	ZHP	Histidine	1 (0.89,1.12)	1.01 (0.88,1.18)	0.79 (0.7,0.87)	0.75 (0.64,0.84)	3.92E-10	1.18E-09	1.00E+00	1.00E-05	2.15E-06	HNDVDQJCIGZPNO-YFKPBYRVSA-N
110	ZHP	3-Methylhistidine	1 (0.91,1.11)	0.93 (0.84,1.02)	0.88 (0.81,0.95)	0.94 (0.86,1.02)	1.26E-04	1.14E-04	5.75E-01	2.32E-04	5.22E-01	JDHILDINMRGULE-LURJTMIESA-N
111	ZHP	1-Methylhistidine	1 (0.72,1.38)	1.08 (0.75,1.51)	0.84 (0.66,1.17)	1.08 (0.83,1.46)	9.01E-02	3.90E-02	9.35E-01	3.54E-01	9.60E-01	JDHILDINMRGULE-LURJTMIESA-N
112	ZHP	Homoarginine	1 (0.79,1.29)	1.07 (0.74,1.27)	0.83 (0.66,0.97)	0.71 (0.55,0.93)	1.93E-03	1.36E-03	9.06E-01	4.45E-02	2.88E-03	QUOGESRFPZDMMT-YFKPBYRVSA-N
113	ZHP	N6-Methyl-lysine	0.99 (0.7,1.42)	0.82 (0.57,1.32)	0.75 (0.57,1.11)	0.72 (0.5,1.05)	2.09E-01	7.72E-02	9.29E-01	3.95E-01	1.96E-01	PQNASZJZHFPQLE-LURJTMIESA-N
114	ZHP	N,N-Dimethyl-lysine	1 (0.86,1.18)	1 (0.82,1.34)	1.05 (0.9,1.26)	0.98 (0.84,1.21)	8.91E-01	2.17E-01	9.64E-01	1.00E+00	9.90E-01	XXEWFEBMSGLYBY-ZETCQYMHSA-N
115	ZHP	Lysine	1 (0.76,1.33)	0.87 (0.66,1.16)	0.85 (0.71,1.07)	0.87 (0.66,1.15)	2.22E-01	8.11E-02	4.72E-01	2.29E-01	2.46E-01	KDXKERNSBIXSRK-YFKPBYRVSA-N
116	ZHP	N,N,N-Trimethyl-lysine	1 (0.85,1.17)	0.99 (0.89,1.15)	0.95 (0.88,1.11)	1.09 (0.94,1.27)	3.60E-01	1.13E-01	9.95E-01	1.00E+00	4.97E-01	MXNRLFUSFKVQSK-QMMMGPOBSA-N
117	ZHP	Anserine	1 (0.55,1.82)	0.83 (0.49,1.38)	0.59 (0.37,0.99)	0.73 (0.43,1.26)	4.81E-02	2.26E-02	5.55E-01	2.82E-02	3.92E-01	MYYIAHXIVFADCU-QMMMGPOBSA-N
118	ZHP	Carnosine	1 (0.81,1.21)	0.89 (0.75,1.1)	0.7 (0.6,0.85)	0.73 (0.61,0.88)	3.66E-05	3.90E-05	4.82E-01	7.01E-05	2.10E-03	CQOVPNPJLQNMDC-ZETCQYMHSA-N
119	ZHP	2-Aminobenzoic acid	1 (0.86,1.15)	1.06 (0.93,1.24)	1.15 (0.99,1.27)	1.19 (1.03,1.38)	1.02E-01	4.27E-02	8.36E-01	1.26E-01	1.61E-01	RWZYAGGXGHYGMB-UHFFFAOYSA-N
120	ZHP	Methyl-hippuric acid	1 (0.67,1.48)	0.84 (0.63,1.21)	1.03 (0.74,1.38)	1.04 (0.74,1.37)	8.74E-01	2.15E-01	8.86E-01	9.99E-01	1.00E+00	XTKVNQKOTKPCKM-UHFFFAOYSA-N
121	ZHP	3-Methyloxyindole	1 (0.58,1.65)	0.61 (0.33,0.97)	0.99 (0.59,1.42)	0.7 (0.42,1.23)	6.48E-02	2.94E-02	2.23E-01	1.00E+00	5.12E-01	BBZCPUCZKLTAJQ-UHFFFAOYSA-N
122	ZHP	Acetyl-cysteine	1 (0.86,1.18)	0.96 (0.83,1.2)	0.98 (0.85,1.13)	1.22 (0.99,1.53)	1.23E-01	4.96E-02	9.93E-01	9.97E-01	1.94E-01	PWKSKIMOESPYIA-BYPYZUCNSA-N
123	ZHP	Cortisol	1 (0.64,1.53)	0.86 (0.58,1.37)	1.09 (0.78,1.64)	1.21 (0.79,2.06)	1.19E-02	6.97E-03	9.98E-01	7.80E-02	1.75E-01	JYGXADMDTFJGBT-VWUMJDOOSA-N
124	ZHP	Hexaethylene glycol	1 (0.84,1.18)	1.02 (0.91,1.19)	1.07 (0.94,1.24)	1.05 (0.91,1.27)	4.54E-01	1.34E-01	6.91E-01	4.15E-01	5.36E-01	IIRDTKBZINWQAW-UHFFFAOYSA-N
125	ZHP	N-Acetyl-tyrosine	1 (0.86,1.17)	0.93 (0.76,1.14)	1.23 (1.05,1.43)	1.67 (1.36,1.96)	2.07E-09	5.27E-09	9.96E-01	9.83E-03	1.86E-07	CAHKINHBCWCHCF-JTQLQIEISA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
126	ZHP	Decanoyl-carnitine (C10:0)	1 (0.83,1.23)	0.85 (0.69,1.03)	0.69 (0.58,0.83)	0.76 (0.64,0.92)	1.93E-05	2.20E-05	4.17E-01	1.57E-05	2.78E-02	LZOSYCMHQXPBFU-OAHLLOKOSA-N
127	ZHP	Octanoyl-carnitine (C8:0)	1 (0.85,1.21)	0.82 (0.68,1.04)	0.68 (0.59,0.79)	0.79 (0.65,0.97)	6.61E-08	1.21E-07	2.98E-01	1.09E-07	4.42E-02	CXTATJFJDMJMIY-CYBMUJFWSA-N
128	ZHP	Nudifloramide	1 (0.87,1.16)	1.03 (0.92,1.23)	1 (0.88,1.21)	0.97 (0.82,1.17)	7.08E-01	1.83E-01	8.42E-01	9.86E-01	9.91E-01	JLQSXXWTCJPCBC-UHFFFAOYSA-N
129	ZHP	Hexanoyl-carnitine (C6:0)	1 (0.89,1.14)	0.97 (0.84,1.12)	0.9 (0.8,1.01)	1.01 (0.84,1.23)	6.10E-02	2.80E-02	1.00E+00	4.26E-01	8.83E-01	VVPRQWTYSNDTEA-LLVKDONJSA-N
130	ZHP	N-Acetyl-threonine	1 (0.88,1.14)	1.11 (0.98,1.25)	1.19 (1.06,1.3)	1.04 (0.91,1.16)	4.84E-02	2.25E-02	3.87E-01	8.66E-02	9.87E-01	PEDXUVCGOLSNLQ-WUJLRWPWSA-N
131	ZHP	Omeprazole	1 (0.75,1.28)	0.77 (0.59,1.09)	1.3 (0.97,1.71)	1.65 (1.18,2.07)	2.52E-06	3.15E-06	7.11E-01	5.01E-02	1.03E-03	SUBDBMMJDZJVOS-UHFFFAOYSA-N
132	ZHP	N-Acetyl-serine	1 (0.88,1.16)	0.98 (0.87,1.16)	0.92 (0.84,1.05)	0.89 (0.8,1.04)	5.23E-01	1.48E-01	9.83E-01	9.77E-01	7.02E-01	JJIHLJJYMXLCOY-UHFFFAOYSA-N
133	ZHP	3-Ureidopropionic acid	1 (0.93,1.08)	1.08 (0.97,1.26)	1.06 (0.99,1.14)	1.09 (0.98,1.18)	1.09E-01	4.51E-02	1.58E-01	4.95E-01	1.54E-01	JSJWCHRYRHKBBW-UHFFFAOYSA-N
134	ZHP	Adipoyl-carnitine (C6:0-COOH)	1 (0.85,1.19)	1.22 (1.01,1.42)	1.23 (1.07,1.44)	1.33 (1.14,1.61)	7.10E-04	5.73E-04	6.48E-02	5.39E-03	3.91E-04	BSVHAXJKBCWVDA-SNVBAGLBSA-N
135	ZHP	5-Acetylamino-6-amino-3-methyluracil	1 (0.77,1.31)	0.77 (0.56,1.01)	1.1 (0.84,1.34)	1.36 (1.06,1.77)	3.78E-04	3.21E-04	4.66E-01	6.31E-01	3.28E-02	POQOTWQIYYNXAT-UHFFFAOYSA-N
136	ZHP	Xanthosine	1 (0.9,1.1)	1.09 (0.97,1.24)	1.04 (0.95,1.13)	1.08 (0.93,1.19)	5.95E-01	1.59E-01	6.44E-01	8.98E-01	6.73E-01	UBORTCNDUKBEOP-UUOKFMHZSA-N
137	ZHP	5-Aminovaleric acid betaine	1 (0.59,1.84)	0.95 (0.6,1.85)	0.79 (0.5,1.24)	0.8 (0.52,1.39)	4.05E-01	1.22E-01	9.99E-01	4.68E-01	9.24E-01	CDLVFVFTRQPQFU-UHFFFAOYSA-N
138	ZHP	Glutaryl-carnitine (C5:0-COOH)	1 (0.89,1.12)	1.06 (0.9,1.14)	0.94 (0.83,1.03)	1.02 (0.89,1.1)	2.80E-01	9.75E-02	9.64E-01	6.65E-01	1.00E+00	NXJAXUYOQLTISD-SECBINFHSA-N
139	ZHP	3-Hydroxypyridine	1 (0.74,1.43)	0.78 (0.62,1.03)	1.1 (0.87,1.42)	1.69 (1.29,2.2)	1.47E-06	1.91E-06	4.55E-01	3.41E-01	8.11E-04	GRFNBEZIAWKNCO-UHFFFAOYSA-N
140	ZHP	Leucine	1 (0.85,1.18)	1.02 (0.85,1.19)	0.91 (0.79,1.06)	0.9 (0.76,1.06)	4.61E-01	1.34E-01	9.96E-01	5.39E-01	6.69E-01	ROHFNLRQFUQHCH-YFKPBYRVSA-N
141	ZHP	4-Aminobutyric acid betaine	1 (0.79,1.27)	0.82 (0.68,1.04)	0.59 (0.47,0.72)	0.7 (0.51,0.95)	3.28E-09	7.75E-09	4.80E-01	1.54E-08	4.93E-03	JHPNVNIEXXLNTR-UHFFFAOYSA-N
142	ZHP	Isoleucine	1 (0.76,1.33)	1.09 (0.85,1.61)	0.98 (0.78,1.28)	1.13 (0.77,1.55)	7.95E-01	1.98E-01	8.15E-01	9.98E-01	9.73E-01	AGPKZVBTJJNPAG-WHFBIAKZSA-N
143	ZHP	Salbutamol	1 (0.58,1.65)	14.23 (4.32,28.65)	12.61 (6.78,18.89)	11.64 (5.54,21.83)	5.46E-12	2.26E-11	4.06E-06	7.43E-12	5.03E-09	NDAUXUAQIAJITI-UHFFFAOYSA-N
144	ZHP	Methionine	1 (0.85,1.17)	1.07 (0.89,1.25)	0.95 (0.83,1.06)	0.94 (0.79,1.08)	2.98E-02	1.53E-02	9.94E-01	9.81E-02	1.09E-01	FFEARJCKVFRZRR-BYPYZUCNSA-N
145	ZHP	Pipecolic acid betaine	1 (0.77,1.3)	0.86 (0.65,1.2)	0.89 (0.74,1.1)	1.09 (0.78,1.41)	7.20E-01	1.85E-01	9.39E-01	8.62E-01	9.99E-01	XULZWQRXYTVUTE-ZETCQYMHSA-N
146	ZHP	Pyrrolidine	1 (0.96,1.04)	1.04 (1,1.09)	1.01 (0.97,1.05)	1 (0.95,1.05)	2.99E-01	1.01E-01	3.72E-01	9.44E-01	1.00E+00	RWRDLPDLKQPQOW-UHFFFAOYSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
147	ZHP	3-Hydroxykynurenine	1 (0.81,1.25)	1.13 (0.95,1.49)	1.25 (1.04,1.53)	1.32 (1.02,1.69)	1.90E-02	1.05E-02	2.54E-01	1.29E-02	5.09E-02	VCKPUUFAIGNJHC-UHFFFAOYSA-N
148	ZHP	Alanine betaine	1 (0.72,1.37)	1.1 (0.88,1.44)	0.91 (0.73,1.24)	1.22 (0.96,1.57)	3.18E-01	1.04E-01	8.90E-01	9.93E-01	6.59E-01	CJKONRHMUGBAQI-UHFFFAOYSA-N
149	ZHP	Betonicine	1 (0.57,1.86)	0.7 (0.39,1.23)	0.86 (0.49,1.21)	0.4 (0.2,0.65)	1.17E-02	6.91E-03	6.44E-01	4.11E-01	6.33E-03	MUNWAHDYFVYIKH-RITPCOANSA-N
150	ZHP	Sucrose (disaccharide)	1 (0.73,1.37)	1.05 (0.75,1.5)	1.27 (1.02,1.66)	1.3 (1.03,1.73)	1.56E-03	1.13E-03	7.64E-01	4.04E-03	1.18E-02	CZMRCDWAGMRECN-UGDNZRGBSA-N
151	ZHP	Alliin	1 (0.57,1.77)	1.17 (0.65,1.9)	0.86 (0.5,1.31)	0.76 (0.36,1.63)	3.08E-01	1.02E-01	8.75E-01	7.98E-01	9.21E-01	XUHLIQGRKRUKPH-DYEAUMGKSA-N
152	ZHP	N1-Methyladenosine	1 (0.9,1.1)	1.1 (0.97,1.22)	1.2 (1.09,1.29)	1.14 (1.01,1.33)	7.77E-04	6.19E-04	5.65E-01	8.92E-04	1.54E-02	GFYLSDSUCHVORB-IOSLPCCCSA-N
153	ZHP	5-Methylcytosine	1 (0.92,1.07)	1.06 (0.97,1.15)	1.09 (1.02,1.17)	1.17 (1,1.29)	2.28E-02	1.23E-02	4.56E-01	4.09E-02	2.25E-02	LRSASMSXMSNRBT-UHFFFAOYSA-N
154	ZHP	Ethanolamine	1 (0.92,1.09)	0.99 (0.93,1.08)	0.91 (0.86,0.98)	0.85 (0.8,0.94)	1.62E-06	2.06E-06	1.00E+00	1.47E-03	1.40E-04	HZAXFHJVJLSVMW-UHFFFAOYSA-N
155	ZHP	Phosphorylcholine	1 (0.68,1.42)	0.87 (0.62,1.19)	1.14 (0.86,1.54)	1.09 (0.81,1.58)	2.92E-01	9.96E-02	9.63E-01	6.50E-01	8.15E-01	YHHSONZFOIEMCP-UHFFFAOYSA-N
156	ZHP	Ornithine	1 (0.93,1.07)	1 (0.95,1.08)	1.05 (1,1.13)	1.07 (1,1.17)	3.59E-01	1.13E-01	9.95E-01	6.76E-01	3.69E-01	AHLPHDHHMVZTML-UHFFFAOYSA-N
157	ZHP	5-Hydroxylysine	1 (0.87,1.14)	1.02 (0.88,1.15)	0.98 (0.87,1.11)	1 (0.88,1.19)	9.04E-01	2.20E-01	9.90E-01	9.88E-01	8.83E-01	YSMODUONRAFBET-UHFFFAOYSA-N
158	ZHP	Cortisone metabolite	1 (0.84,1.18)	0.94 (0.79,1.15)	1.02 (0.85,1.23)	0.93 (0.74,1.34)	3.54E-01	1.13E-01	9.96E-01	5.65E-01	9.73E-01	MFYSYFVPBJMHGN-ZPOLXVRWSA-N
159	ZHP	Dihydrocortisol	1 (0.83,1.21)	0.88 (0.71,1.14)	0.41 (0.33,0.5)	0.32 (0.24,0.53)	1.36E-22	1.50E-21	7.17E-01	5.31E-14	3.06E-13	
160	ZHP	Salbutamol metabolite 2 (salbutamol fragment)	1 (0.88,1.13)	0.98 (0.85,1.19)	0.95 (0.87,1.05)	0.96 (0.84,1.08)	9.31E-01	2.24E-01	1.00E+00	9.95E-01	9.28E-01	
161	ZHP	Dihydrotestosterone metabolite 1	1 (0.88,1.16)	0.92 (0.77,1.11)	0.56 (0.5,0.64)	0.57 (0.5,0.64)	1.11E-27	1.84E-26	6.26E-01	3.51E-14	1.53E-12	
162	ZHP	Verapamil	1 (0.75,1.32)	1.25 (0.92,1.6)	1.13 (0.92,1.41)	1.05 (0.85,1.32)	2.33E-01	8.38E-02	3.34E-01	5.46E-01	9.99E-01	
163	ZHP	Dihydrotestosterone metabolite 2	1 (0.82,1.22)	0.89 (0.76,1.07)	0.56 (0.47,0.64)	0.58 (0.47,0.71)	5.75E-29	1.27E-27	8.71E-01	3.26E-14	1.54E-11	
164	ZHP	Tetradecadienyl-carnitine (C14:2)	1 (0.59,1.68)	0.9 (0.59,1.53)	1.08 (0.75,1.71)	1.1 (0.74,1.85)	6.35E-01	1.67E-01	9.63E-01	9.38E-01	5.79E-01	
165	ZHP	Undecanoyl-carnitine (C11:0)	1 (0.7,1.51)	0.71 (0.49,0.97)	0.49 (0.35,0.63)	0.55 (0.39,0.75)	4.66E-11	1.62E-10	6.77E-02	5.57E-11	3.02E-05	
166	ZHP	Dodecenoyl-carnitine (C12:1)	1 (0.79,1.24)	0.95 (0.73,1.23)	0.98 (0.8,1.17)	1 (0.78,1.23)	5.03E-01	1.45E-01	6.71E-01	5.39E-01	9.76E-01	
167	ZHP	Undecenoyl-carnitine (C11:1)	1 (0.75,1.28)	0.74 (0.5,1.16)	0.42 (0.32,0.54)	0.53 (0.35,0.7)	1.79E-11	6.58E-11	2.74E-01	1.11E-10	1.07E-04	

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
168	ZHP	Nonanoyl-carnitine (C9:0)	1 (0.78,1.3)	0.95 (0.76,1.19)	0.78 (0.68,1)	0.93 (0.75,1.19)	1.78E-02	9.89E-03	6.94E-01	1.45E-02	5.80E-01	
169	ZHP	Decenoyl-carnitine (C10:1)	1 (0.84,1.18)	0.98 (0.78,1.22)	0.77 (0.66,0.87)	0.85 (0.7,1.03)	1.14E-04	1.05E-04	9.30E-01	3.76E-04	1.39E-01	
170	ZHP	Hydroxydodecenoyl-carnitine (C12:1-OH)	1 (0.81,1.24)	0.99 (0.77,1.25)	0.77 (0.62,0.89)	0.83 (0.67,0.98)	6.02E-05	6.22E-05	9.97E-01	5.71E-04	2.67E-01	
171	ZHP	Decadienoyl-carnitine (C10:2)	1 (0.78,1.35)	0.8 (0.62,1.06)	0.83 (0.66,0.98)	0.87 (0.68,1.09)	1.09E-01	4.48E-02	5.32E-01	7.12E-02	6.11E-01	
172	ZHP	Decatrienoyl-carnitine (C10:3)	1 (0.85,1.19)	0.93 (0.7,1.19)	0.75 (0.63,0.89)	0.72 (0.58,0.93)	8.61E-04	6.78E-04	9.95E-01	6.04E-03	3.99E-02	
173	ZHP	Heptanoyl-carnitine (C7:0)	1 (0.77,1.25)	0.92 (0.75,1.2)	0.72 (0.63,0.88)	0.78 (0.65,1.02)	4.48E-07	6.73E-07	7.81E-01	2.46E-06	1.82E-02	
174	ZHP	Ketodecanoyl-carnitine (C10:0=O)	1 (0.78,1.27)	1.08 (0.89,1.26)	0.76 (0.61,0.88)	0.84 (0.68,0.95)	9.05E-08	1.62E-07	9.35E-01	8.48E-05	1.63E-02	
175	ZHP	Propenoyl-carnitine (C3:1)	1 (0.89,1.12)	0.88 (0.77,1.03)	0.95 (0.86,1.06)	1.58 (1.18,2.43)	7.33E-09	1.56E-08	2.48E-01	9.12E-01	3.95E-04	
176	ZHP	5-Hydroxyomeprazole	1 (0.58,1.71)	1.02 (0.62,1.75)	2.1 (1.43,3.34)	2.02 (1.05,5.37)	1.45E-04	1.28E-04	9.20E-01	1.88E-03	2.90E-03	
177	ZHP	Heptenoyl-carnitine (C7:1)	1 (0.82,1.24)	1.07 (0.84,1.32)	0.98 (0.86,1.17)	1 (0.76,1.3)	6.73E-01	1.75E-01	9.64E-01	9.30E-01	9.72E-01	
178	ZHP	Hexenoyl-carnitine (C6:1)	1 (0.81,1.27)	1.01 (0.87,1.22)	0.79 (0.67,0.97)	0.77 (0.64,0.98)	1.39E-02	7.93E-03	1.00E+00	5.66E-02	3.38E-01	
179	ZHP	Tiglyl-carnitine (C5:1)	1 (0.83,1.19)	0.98 (0.82,1.21)	0.79 (0.7,0.92)	0.87 (0.77,1.02)	2.55E-04	2.22E-04	9.97E-01	1.86E-03	5.03E-01	
180	ZHP	Hydroxyhexanoyl-carnitine (C6:0-OH) 1	1 (0.7,1.46)	0.87 (0.59,1.12)	0.5 (0.35,0.66)	0.63 (0.41,0.96)	4.60E-07	6.76E-07	6.16E-01	1.32E-06	1.60E-02	
181	ZHP	Hydroxydecanoyl-carnitine (C10:0-OH)	1 (0.88,1.12)	1.04 (0.88,1.16)	0.87 (0.77,0.94)	0.99 (0.84,1.16)	7.17E-03	4.47E-03	1.00E+00	1.38E-01	9.23E-01	
182	ZHP	Hydroxyoctanoyl-carnitine (C8:0-OH)	1 (0.82,1.23)	0.85 (0.69,1.01)	0.6 (0.49,0.71)	0.69 (0.55,0.83)	4.32E-10	1.24E-09	2.42E-01	1.04E-09	1.07E-03	
183	ZHP	Isobar of Glutaryl-carnitine (C5:0-OOH)	1 (0.63,1.51)	0.73 (0.46,1.01)	0.26 (0.16,0.38)	0.36 (0.21,0.53)	3.90E-13	1.98E-12	2.01E-01	3.13E-12	4.75E-05	
184	ZHP	Nitrophenylalanine	0.99 (0.55,1.8)	0.99 (0.66,1.54)	1.99 (1.24,2.72)	2.12 (1.18,3.9)	1.78E-07	2.80E-07	1.00E+00	5.32E-05	2.11E-03	
185	ZHP	Butenyl-carnitine (C4:1)	1 (0.84,1.22)	0.98 (0.86,1.18)	0.82 (0.73,0.98)	1.37 (1.08,1.64)	9.86E-12	3.84E-11	9.97E-01	1.65E-02	3.70E-03	
186	ZHP	Hydroxyheptanoyl-carnitine (C7:0-OH)	1 (0.91,1.09)	1.03 (0.89,1.16)	0.81 (0.74,0.88)	0.85 (0.77,0.94)	7.56E-06	9.09E-06	1.00E+00	2.74E-04	1.58E-01	
187	ZHP	Acetaminophen metabolite	1 (0.73,1.36)	1.09 (0.8,1.36)	1.51 (1.13,1.86)	1.87 (1.27,2.58)	1.31E-06	1.73E-06	6.72E-01	1.21E-04	1.68E-05	
188	ZHP	Hydroxyhexanoyl-carnitine (C6:0-OH) 2	1.01 (0.79,1.26)	1.01 (0.8,1.27)	0.85 (0.72,1.04)	0.98 (0.77,1.25)	7.40E-02	3.29E-02	9.42E-01	3.89E-01	1.00E+00	

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
189	ZHP	Pimelyl-carnitine (C7:0-OOH)	1 (0.84,1.2)	0.99 (0.82,1.15)	1.03 (0.88,1.16)	1.01 (0.84,1.28)	5.63E-01	1.54E-01	9.96E-01	9.98E-01	6.15E-01	
190	ZHP	2-Benzoxazolol	1 (0.85,1.21)	1.03 (0.87,1.26)	1.07 (0.93,1.27)	1.25 (1.05,1.52)	1.53E-02	8.58E-03	9.21E-01	8.32E-01	1.74E-02	
191	ZHP	Hydroxyisovaleryl-carnitine (C5:0-OH)	1 (0.84,1.18)	1.05 (0.86,1.22)	0.83 (0.73,0.96)	0.96 (0.81,1.12)	6.98E-05	7.00E-05	9.93E-01	3.18E-03	8.78E-01	
192	ZHP	Salbutamol metabolite1	1 (0.88,1.15)	1.87 (1.38,2.88)	2.01 (1.55,2.48)	1.77 (1.35,2.76)	4.74E-13	2.09E-12	2.91E-06	4.12E-13	2.30E-09	
193	ZHP	Prednisone metabolite 2	1 (0.84,1.2)	1.09 (0.86,1.36)	1.3 (1.11,1.57)	2.2 (1.74,2.71)	5.59E-09	1.23E-08	7.33E-01	7.85E-03	1.00E-08	
194	ZHP	N-Ornithyl-taurine	1 (0.81,1.23)	0.8 (0.65,1.04)	0.58 (0.5,0.71)	0.64 (0.5,0.84)	7.95E-07	1.12E-06	5.50E-01	1.63E-06	2.50E-02	
195	ZHP	Hydroxybutyryl-carnitine (C4:0-OH)	1 (0.86,1.15)	0.8 (0.64,1)	0.63 (0.51,0.8)	0.8 (0.62,1)	1.11E-04	1.03E-04	6.42E-01	1.41E-04	1.94E-01	
196	ZHP	Thiophanate-methyl	1 (0.65,1.57)	0.82 (0.55,1.26)	1.98 (1.33,3.05)	2.26 (1.09,9.86)	1.35E-08	2.79E-08	9.84E-01	3.33E-05	8.30E-04	
197	ZHP	Succinyl-carnitine (C4:0-OOH)	1 (0.83,1.16)	1.07 (0.94,1.22)	1.01 (0.88,1.15)	1.06 (0.93,1.22)	6.00E-01	1.59E-01	9.06E-01	9.98E-01	6.83E-01	
198	ZHP	Malonyl-carnitine (C2:0-OOH)	1 (0.8,1.23)	0.98 (0.77,1.24)	0.9 (0.75,1.03)	1.03 (0.84,1.18)	9.46E-02	4.01E-02	1.00E+00	2.23E-01	9.64E-01	
199	ZHP	Hydroxypropionyl-carnitine (C3:0-OH)	1 (0.84,1.18)	1.15 (0.98,1.38)	1.27 (1.12,1.46)	1.62 (1.34,2.01)	6.10E-07	8.77E-07	3.44E-01	4.19E-03	2.53E-07	
200	ZHP	Hepteneoylglycine	1 (0.65,1.54)	0.91 (0.56,1.4)	0.75 (0.51,1)	0.99 (0.63,1.42)	1.46E-03	1.10E-03	8.78E-01	5.21E-03	9.00E-01	
201	ZHP	Sulfamethoxazole metabolite	1 (0.75,1.33)	1.09 (0.86,1.44)	1.33 (1.08,1.73)	1.5 (1.05,2.06)	1.23E-03	9.35E-04	8.60E-01	6.15E-03	8.05E-03	
202	ZHN	Hypoxanthine	1 (0.76,1.33)	1.29 (0.92,1.77)	1 (0.8,1.28)	0.94 (0.7,1.28)	4.03E-02	1.99E-02	5.79E-01	7.56E-01	5.40E-01	FDGQSTZJBFJUBT-UHFFFAOYSA-N
203	ZHN	Glutamic acid	1 (0.86,1.16)	0.98 (0.9,1.15)	1.12 (1.02,1.3)	1.14 (1.04,1.33)	2.13E-03	1.44E-03	9.86E-01	3.39E-02	9.13E-03	WHUUTDBJXJRKMK-VKHMYHEASA-N
204	ZHN	Tartaric acid	1 (0.54,1.89)	0.75 (0.41,1.79)	1.01 (0.64,1.63)	0.79 (0.4,1.39)	7.16E-01	1.84E-01	7.69E-01	9.76E-01	8.20E-01	FEWJPZIEWOKRBE-JCYAYHJZSA-N
205	ZHN	Acetaminophen	1 (0.4,2.27)	1.2 (0.43,4.13)	2.81 (1.2,4.47)	1.1 (0.44,3.91)	3.72E-02	1.88E-02	7.85E-01	2.92E-02	4.96E-01	RZVAJINKPMORJF-UHFFFAOYSA-N
206	ZHN	Xanthine	1 (0.81,1.19)	1.06 (0.85,1.23)	1.08 (0.87,1.29)	0.87 (0.71,0.99)	7.63E-02	3.36E-02	9.22E-01	6.62E-01	6.87E-01	LRFVTYWOQMYALW-UHFFFAOYSA-N
207	ZHN	Kynurenic acid	1 (0.92,1.1)	1.07 (0.95,1.19)	0.91 (0.83,0.98)	0.93 (0.84,1.05)	1.87E-03	1.34E-03	6.82E-01	9.58E-02	6.84E-01	HCZHHEIFKROPDY-UHFFFAOYSA-N
208	ZHN	Gluconic acid	1 (0.9,1.1)	1.07 (0.97,1.22)	1.2 (1.09,1.3)	1.22 (1.09,1.36)	1.96E-05	2.20E-05	5.93E-01	7.66E-04	6.36E-05	RGHNJXZEOKUKBD-SQOUGZDYSA-N
209	ZHN	Serine	1 (0.89,1.1)	1.04 (0.91,1.16)	0.87 (0.79,0.95)	0.87 (0.77,0.94)	2.92E-05	3.17E-05	9.25E-01	6.58E-04	1.19E-03	MTCFGRXMJLQNBG-REOHCLBHSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	Method	Metabolites	HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)	KW p-value	FDR	MMA_HC	SAns_HC	SAs_HC	INCHIKEY
210	ZHN	Threonine	1 (0.71,1.38)	1.2 (0.82,1.55)	1.07 (0.8,1.34)	0.88 (0.66,1.2)	3.98E-01	1.21E-01	9.75E-01	9.96E-01	6.06E-01	AYFVYJQAPQTCCC-GBXIJSLDSA-N
211	ZHN	Taurine	1 (0.7,1.38)	0.93 (0.56,1.41)	0.81 (0.62,1.1)	0.93 (0.57,1.44)	5.64E-01	1.54E-01	1.00E+00	7.06E-01	1.00E+00	XOAAWQZATWQOTB-UHFFFAOYSA-N
212	ZHN	Methylxanthine	1 (0.85,1.19)	0.76 (0.62,0.96)	1 (0.89,1.14)	1.18 (1,1.38)	8.10E-05	7.88E-05	1.15E-01	9.86E-01	6.89E-02	MVOYJPOZRLFTCP-UHFFFAOYSA-N
213	ZHN	N-Acetylcarnosine	1 (0.8,1.26)	0.92 (0.77,1.07)	0.64 (0.54,0.73)	0.63 (0.52,0.77)	4.23E-13	2.00E-12	5.14E-01	1.12E-10	3.97E-07	BKAYIFDRRZZKNF-SECBINFHSA-N
214	ZHN	5-Acetylamino-6-formylamino-3-methyluracil	1 (0.76,1.33)	0.95 (0.59,1.3)	1.06 (0.85,1.34)	1.41 (1.09,1.86)	4.50E-02	2.16E-02	1.00E+00	7.39E-01	7.21E-02	RDZNZFGKEVDNPK-UHFFFAOYSA-N
215	ZHN	Histidine	1 (0.83,1.2)	0.98 (0.81,1.2)	0.7 (0.6,0.83)	0.68 (0.56,0.82)	3.33E-10	1.05E-09	1.00E+00	7.53E-06	1.98E-06	HNDVDQJCIGZPNO-YFKPBYRVSA-N
216	ZHN	Mannitol	1 (0.78,1.31)	0.97 (0.77,1.18)	0.96 (0.81,1.13)	1.08 (0.85,1.48)	3.03E-01	1.02E-01	7.88E-01	9.87E-01	7.98E-01	FBPFZTCFMRRESA-KVTDHHQDSA-N
217	ZHN	Inosine	1 (0.84,1.21)	1.06 (0.82,1.28)	1.04 (0.9,1.2)	1.04 (0.85,1.28)	7.28E-01	1.86E-01	1.00E+00	8.74E-01	7.84E-01	UGQMRVRMYYASKQ-KQYNXXCUSA-N
218	ZHN	Xanthosine	1 (0.51,2.25)	0.82 (0.4,1.73)	0.98 (0.63,2.03)	1.55 (0.85,3.35)	9.13E-02	3.92E-02	1.00E+00	9.48E-01	1.47E-01	UBORTCNDUKBEOP-UUOKFMHZSA-N
219	ZHN	Methyluric acid	1 (0.82,1.2)	0.77 (0.58,0.94)	1.14 (0.97,1.31)	1.29 (1.09,1.55)	1.56E-07	2.52E-07	2.06E-01	1.75E-01	1.59E-03	YHNNPKUFPWLTOP-UHFFFAOYSA-N
220	ZHN	Dimethylxanthine	1 (0.57,1.76)	0.46 (0.28,0.87)	0.86 (0.58,1.6)	0.76 (0.49,1.67)	4.43E-02	2.14E-02	8.23E-02	9.93E-01	1.00E+00	QUNWUDVFRNGTCO-UHFFFAOYSA-N
221	ZHN	Glucose	1 (0.75,1.34)	0.73 (0.62,0.97)	0.95 (0.79,1.2)	1.23 (0.96,1.69)	1.41E-04	1.26E-04	1.50E-01	9.52E-01	7.27E-02	WQZGKKKJIJFFOK-DVKNGEFBSA-N
222	ZHN	Glycolic acid	1 (0.66,1.68)	0.89 (0.63,1.29)	0.74 (0.57,1.14)	0.67 (0.5,1.05)	1.92E-01	7.22E-02	9.99E-01	3.59E-01	3.69E-01	AEMRFAOFKBGASW-UHFFFAOYSA-N
223	ZHN	Galacturonic acid	1 (0.9,1.11)	1.08 (0.98,1.19)	1.15 (1.06,1.28)	1.25 (1.13,1.38)	9.91E-08	1.68E-07	4.46E-01	1.36E-04	2.24E-07	AEMOLEFTQBMNLQ-WAXACMCWSA-N
224	ZHN	Saccharin	1 (0.52,1.95)	1.54 (0.63,3.72)	1.36 (0.85,2.47)	1.67 (0.71,3.59)	4.02E-01	1.21E-01	4.78E-01	4.61E-01	4.74E-01	CVHZOJJKTDOEJC-UHFFFAOYSA-N
225	ZHN	Dideoxy-imino-ribitol	1 (0.88,1.15)	1.02 (0.84,1.18)	1.11 (0.99,1.26)	1.27 (1.1,1.45)	6.43E-05	6.54E-05	9.27E-01	3.10E-02	1.12E-04	
226	ZHN	Testosterone glucuronide	1 (0.84,1.19)	0.81 (0.68,1)	0.27 (0.22,0.33)	0.24 (0.18,0.32)	3.01E-34	9.95E-33	7.46E-01	3.41E-14	4.27E-14	
227	ZHN	Androstanediol glucuronide	1 (0.59,1.68)	0.74 (0.45,1.18)	0.29 (0.18,0.45)	0.37 (0.23,0.62)	1.41E-15	7.77E-15	6.71E-01	1.22E-12	2.73E-06	
228	ZHN	Hydroxyandrosterone glucuronide	1 (0.81,1.27)	1.05 (0.83,1.3)	0.47 (0.37,0.62)	0.46 (0.34,0.65)	6.98E-19	5.13E-18	9.98E-01	9.08E-12	6.06E-08	
229	ZHN	Hydroxyandrostane glucuronide	1 (0.79,1.28)	0.88 (0.71,1.05)	0.39 (0.31,0.47)	0.45 (0.34,0.59)	1.76E-24	2.33E-23	6.98E-01	5.13E-14	1.05E-08	

Idx	Method	Metabolites	Fold Change				KW p-value	FDR	Post hoc pairwise comparison			INCHIKEY
			HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)			MMA_HC	SAns_HC	SAs_HC	
230	ZHN	Pregnanediol glucuronide	1 (0.8,1.3)	0.89 (0.69,1.13)	0.37 (0.29,0.5)	0.31 (0.24,0.44)	3.70E-21	3.50E-20	9.01E-01	3.84E-13	9.38E-13	
231	ZHN	Nitrophenylalanine	1 (0.63,1.56)	1.01 (0.64,1.46)	1.9 (1.3,2.63)	2.18 (1.22,3.91)	9.66E-08	1.68E-07	9.97E-01	5.96E-05	1.44E-03	
232	ZHN	Ethyl-glucuronide 2	1 (0.8,1.23)	1.14 (0.92,1.55)	1.11 (0.87,1.29)	1.25 (0.94,1.57)	6.66E-01	1.73E-01	9.39E-01	9.85E-01	6.65E-01	
233	ZHN	Ethyl-glucuronide 1	1 (0.72,1.35)	1 (0.69,1.51)	1.14 (0.86,1.44)	1.4 (0.97,1.94)	2.02E-01	7.51E-02	9.82E-01	9.10E-01	3.49E-01	
234	ZHN	Glyceric acid	1 (0.86,1.19)	0.83 (0.71,1.02)	0.89 (0.77,1.02)	0.75 (0.63,0.89)	4.31E-04	3.61E-04	2.26E-01	6.37E-02	1.31E-04	
235	ZHN	Galactose sulfate	1 (0.93,1.07)	1.14 (1.01,1.21)	1.12 (1.04,1.2)	1.22 (1.1,1.35)	1.43E-05	1.66E-05	7.67E-02	1.65E-03	4.30E-06	
236	ZHN	Indoxyl glucuronide	1 (0.71,1.43)	1.07 (0.88,1.59)	1.28 (1.1,1.86)	1.58 (1.22,2.26)	7.10E-05	7.01E-05	6.40E-01	8.85E-03	6.49E-05	
237	ZHN	Salbutamol sulfate	1 (0.71,1.41)	10.55 (4.22,17.67)	11.69 (7.23,18.58)	10.76 (4.89,17.7)	1.72E-16	1.14E-15	1.43E-08	4.01E-14	1.70E-11	
238	ZHN	Cortisone	1 (0.74,1.36)	0.94 (0.69,1.36)	0.42 (0.32,0.59)	0.38 (0.28,0.57)	1.82E-16	1.09E-15	9.59E-01	4.28E-11	1.39E-08	
239	ZHN	Dehydroepiandrosterone sulfate	1 (0.41,2.44)	0.51 (0.21,1.19)	0.08 (0.04,0.14)	0.08 (0.04,0.18)	1.22E-35	8.07E-34	5.20E-01	4.06E-14	4.26E-14	
240	ZHN	Estrone glucuronide	1 (0.85,1.18)	0.72 (0.58,1.02)	0.34 (0.25,0.43)	0.32 (0.19,0.45)	6.08E-20	5.03E-19	4.13E-01	4.92E-14	1.21E-10	
241	ZHN	Uric acid	1 (0.93,1.06)	1.01 (0.95,1.08)	0.98 (0.94,1.03)	0.95 (0.87,1.02)	4.66E-02	2.20E-02	9.87E-01	7.31E-01	1.05E-01	
242	ZHN	Pseudouridine	1 (0.94,1.06)	1.04 (0.97,1.12)	1 (0.95,1.05)	0.97 (0.91,1.02)	3.74E-02	1.87E-02	3.46E-01	9.93E-01	6.17E-01	
243	R-ZHP	1,3,7-Trimethyluric acid	0.99 (0.65,1.53)	0.74 (0.51,1.13)	1.04 (0.82,1.55)	1.45 (1.06,2.24)	3.32E-03	2.15E-03	4.38E-01	9.78E-01	1.20E-01	BYXCFUMGEBZDDI-UHFFFAOYSA-N
244	R-ZHN	3-Hydroxybutyric acid	1 (0.86,1.17)	0.97 (0.86,1.16)	0.96 (0.86,1.13)	0.95 (0.8,1.11)	8.51E-01	2.12E-01	1.00E+00	9.17E-01	9.60E-01	WHBMMWSBFZVSSR-UHFFFAOYSA-N
245	R-ZHP	3-Hydroxyproline	1 (0.81,1.29)	0.82 (0.67,1.1)	0.93 (0.78,1.18)	0.99 (0.76,1.38)	5.83E-01	1.57E-01	8.65E-01	9.80E-01	9.49E-01	BJBUEDPLEOHJGE-IUYQGCFVSA-N
246	R-ZHP	5-Aminolevulinic acid	1 (0.85,1.16)	1.05 (0.8,1.27)	0.9 (0.77,1.03)	0.97 (0.81,1.15)	4.63E-02	2.20E-02	9.35E-01	5.39E-02	2.89E-01	ZGXJTSGNIOSYLO-UHFFFAOYSA-N
247	R-ZHP	Alanine	1 (0.87,1.15)	1.01 (0.85,1.2)	0.97 (0.85,1.09)	0.98 (0.83,1.14)	8.76E-01	2.15E-01	9.91E-01	8.86E-01	8.94E-01	QNAYBMKLOCPYGJ-REOHCLBHSA-N
248	R-ZHP	Allantoin	1 (0.79,1.23)	1.03 (0.87,1.23)	1.05 (0.9,1.28)	0.97 (0.79,1.18)	3.38E-01	1.09E-01	8.13E-01	8.27E-01	9.35E-01	POJWUDADGALRAB-UHFFFAOYSA-N
249	R-ZHP	alpha-Glutamyltyrosine	1 (0.86,1.18)	0.93 (0.76,1.23)	1.03 (0.91,1.21)	0.85 (0.68,1.05)	2.34E-01	8.37E-02	9.90E-01	9.99E-01	4.33E-01	YSWHPLCDIMUKFE-UHFFFAOYSA-N
250	R-ZHP	Aminocaproic acid	1 (0.7,1.49)	1.44 (0.95,1.94)	1.17 (0.82,1.5)	1.24 (0.88,1.78)	2.46E-01	8.66E-02	2.82E-01	9.89E-01	8.74E-01	SLXKOJJOQWFEFD-UHFFFAOYSA-N

Idx	Method	Metabolites	Fold Change				KW p-value	FDR	Post hoc pairwise comparison			INCHIKEY
			HC (FC to HC)	MMA (FC to HC)	SAns (FC to HC)	SAs (FC to HC)			MMA_HC	SAns_HC	SAs_HC	
251	R-ZHP	Aminovaleric acid	1 (0.66,1.53)	0.81 (0.49,1.36)	0.88 (0.63,1.19)	0.65 (0.43,1.15)	3.91E-01	1.20E-01	7.83E-01	5.54E-01	3.22E-01	JJMDCOVWQOJGCB-UHFFFAOYSA-N
252	R-ZHP	Asparagine	1 (0.85,1.17)	1.07 (0.89,1.23)	0.96 (0.84,1.05)	0.89 (0.76,1.01)	1.95E-03	1.36E-03	9.44E-01	3.09E-01	1.70E-02	DCXYFEDJOCDNAF-REOHCLBHSA-N
253	R-ZHP	Aspartic acid	1 (0.88,1.15)	1.04 (0.88,1.17)	1.07 (0.94,1.22)	1.05 (0.84,1.23)	7.35E-01	1.86E-01	9.78E-01	6.97E-01	9.13E-01	CKLJMWTZIZZHCS-REOHCLBHSA-N
254	R-ZHP	Biopterin	1 (0.84,1.19)	1.02 (0.85,1.18)	0.95 (0.8,1.1)	0.99 (0.86,1.13)	9.73E-01	2.32E-01	1.00E+00	9.87E-01	9.98E-01	LHQIJBMDNUYRAM-DZSWIPIPSA-N
255	R-ZHN	Galacturonic acid	1 (0.89,1.13)	1.07 (0.97,1.2)	1.14 (1.05,1.25)	1.22 (1.12,1.36)	2.50E-07	3.85E-07	4.62E-01	1.77E-04	5.81E-07	IAJILQKETJEXLJ-RSJOWCBRSA-N
256	R-ZHP	gamma-Aminobutyric acid	1 (0.78,1.26)	0.89 (0.69,1.14)	1.08 (0.86,1.38)	0.96 (0.76,1.27)	4.37E-01	1.30E-01	9.49E-01	8.23E-01	1.00E+00	BTCSSZJGUNDROE-UHFFFAOYSA-N
257	R-ZHP	Guanosine	1 (0.75,1.38)	1.14 (0.87,1.6)	1.06 (0.86,1.33)	1.08 (0.79,1.46)	4.25E-01	1.27E-01	3.50E-01	6.82E-01	7.34E-01	NYHBQMYGNKIUIF-UUOKFMHZSA-N
258	R-ZHN	Hydroxyphenylacetic acid	1 (0.44,2.44)	1.49 (0.59,3.3)	1.61 (0.75,2.74)	0.64 (0.27,1.92)	4.30E-02	2.09E-02	7.01E-01	4.44E-01	8.08E-01	XQXPVVBIMDBYFF-UHFFFAOYSA-N
259	R-ZHN	Maltose	1.01 (0.76,1.32)	0.95 (0.65,1.45)	1.35 (1.08,1.84)	1.8 (1.26,2.67)	4.46E-04	3.69E-04	9.48E-01	1.07E-02	2.31E-03	GUBGYTABKSRVRQ-DKBJLJRDSA-N
260	R-ZHN	Mesaconic acid	0.99 (0.79,1.28)	1.06 (0.83,1.26)	0.95 (0.75,1.12)	0.88 (0.69,1.08)	1.69E-01	6.54E-02	9.76E-01	7.29E-01	3.65E-01	HNEGQIOMVPPMNR-NSCUHMNNSA-N
261	R-ZHP	Metanephrine	0.99 (0.87,1.17)	1.19 (0.99,1.42)	0.91 (0.77,1.09)	1.01 (0.84,1.24)	1.53E-01	6.02E-02	8.11E-01	7.29E-01	9.92E-01	JWJCTZKFYGDABJ-UHFFFAOYSA-N
262	R-ZHN	N-Methyl-D-aspartic acid	1 (0.92,1.08)	0.94 (0.85,1.04)	1.01 (0.94,1.09)	1.03 (0.93,1.13)	2.14E-01	7.86E-02	7.33E-01	9.67E-01	7.35E-01	HOKKHZGPKSLGJE-GSVOUGTGSA-N
263	R-ZHP	N-Methylhistamine	1 (0.84,1.17)	1.13 (0.99,1.3)	0.91 (0.82,1.06)	0.99 (0.88,1.16)	7.83E-03	4.75E-03	4.98E-01	3.58E-01	1.00E+00	PHSPJQZRQAJPPF-UHFFFAOYSA-N
264	R-ZHP	Nitrotyrosine	1 (0.93,1.06)	1.07 (0.96,1.14)	1.03 (0.97,1.09)	1.02 (0.95,1.08)	2.84E-01	9.78E-02	2.40E-01	4.62E-01	5.28E-01	FBTSQILOGYXGMD-LURJTMIESA-N
265	R-ZHN	O-Acetylserine	1 (0.87,1.13)	1.01 (0.88,1.15)	0.97 (0.87,1.07)	0.9 (0.81,1.03)	4.01E-01	1.22E-01	9.99E-01	7.53E-01	4.32E-01	VZXPDPZARILFQX-BYPYZUCNSA-N
266	R-ZHP	Octopamine	1 (0.79,1.21)	1.11 (0.93,1.33)	1.1 (0.93,1.3)	1.06 (0.88,1.3)	3.56E-01	1.13E-01	6.06E-01	4.49E-01	9.92E-01	QHGUCRYDKWKLMG-QMMMGPOBSA-N
267	R-ZHP	Paraxanthine	1 (0.7,1.43)	1.13 (0.52,1.64)	1.28 (0.89,1.82)	1.04 (0.62,1.66)	3.44E-01	1.10E-01	9.00E-01	7.87E-01	9.98E-01	YAPQBXQYLJRXSA-UHFFFAOYSA-N
268	R-ZHN	Phenyllactic acid	1 (0.87,1.14)	0.99 (0.88,1.13)	0.97 (0.9,1.11)	0.92 (0.82,1.06)	4.89E-01	1.41E-01	9.80E-01	9.87E-01	8.01E-01	VOXXWSYKYCBWHO-UHFFFAOYSA-N
269	R-ZHP	Phosphoethanolamine	1 (0.66,1.56)	0.64 (0.4,1.07)	0.76 (0.51,1.09)	0.72 (0.45,1.09)	1.12E-01	4.57E-02	1.86E-01	1.17E-01	2.07E-01	SUHOOTKUPISOBE-UHFFFAOYSA-N
270	R-ZHP	Pipecolic acid	1 (0.83,1.18)	1.03 (0.81,1.23)	1.1 (0.92,1.29)	1.07 (0.89,1.27)	4.56E-01	1.33E-01	9.92E-01	5.71E-01	5.61E-01	HXEACLLIILLPRG-UHFFFAOYSA-N
271	R-ZHP	Pyridoxal	1 (0.94,1.07)	1.05 (0.97,1.14)	1.03 (0.97,1.09)	1.02 (0.96,1.12)	4.42E-01	1.31E-01	3.70E-01	7.50E-01	7.31E-01	RADKZDMFGJYCBB-UHFFFAOYSA-N

			Fold Change						Post hoc pairwise comparison			
Idx	**Method**	**Metabolites**	**HC (FC to HC)**	**MMA (FC to HC)**	**SAns (FC to HC)**	**SAs (FC to HC)**	**KW p-value**	**FDR**	**MMA_HC**	**SAns_HC**	**SAs_HC**	**INCHIKEY**
272	R-ZHP	Pyroglutamic acid	1 (0.94,1.06)	1.04 (0.97,1.11)	0.99 (0.93,1.05)	1.02 (0.95,1.12)	3.69E-01	1.15E-01	3.39E-01	9.07E-01	7.50E-01	ODHCTXKNWHHXJC-VKHMYHEASA-N
273	R-ZHP	Pyroglutamylglycine	1 (0.87,1.14)	0.98 (0.89,1.1)	1.09 (0.98,1.25)	1.31 (1.13,1.5)	5.23E-04	4.27E-04	9.84E-01	3.61E-01	3.13E-03	MGEFGYONNZYSPY-UHFFFAOYSA-N
274	R-ZHP	S-Adenosylhomocysteine	1 (0.84,1.18)	1.11 (0.96,1.3)	1.08 (0.94,1.22)	1.14 (0.98,1.35)	1.07E-01	4.45E-02	4.59E-01	8.61E-01	1.24E-01	ZJUKTBDSGOFHSH-WFMPWKQPSA-N
275	R-ZHP	Saccharopine	0.99 (0.79,1.27)	1.18 (0.82,1.64)	1.47 (1.16,1.9)	1.3 (1.09,1.64)	1.47E-03	1.08E-03	6.19E-01	1.60E-03	2.61E-02	ZDGJAHTZVHVLOT-YUMQZZPRSA-N
276	R-ZHP	Sarcosine	1 (0.9,1.1)	1.08 (0.95,1.23)	1.3 (1.17,1.43)	1.42 (1.2,1.69)	3.20E-09	7.84E-09	3.75E-01	3.96E-07	3.86E-07	FSYKKLYZXJSNPZ-UHFFFAOYSA-N
277	R-ZHP	Serotonin	1 (0.73,1.34)	0.89 (0.65,1.14)	1 (0.78,1.25)	1.05 (0.81,1.33)	1.30E-01	5.18E-02	3.09E-01	1.00E+00	9.67E-01	QZAYGJVTTNCVMB-UHFFFAOYSA-N
278	R-ZHP	Tryptamine	1 (0.67,1.43)	0.9 (0.62,1.34)	0.78 (0.55,1)	0.8 (0.55,1.03)	7.73E-03	4.78E-03	8.52E-01	8.41E-03	1.94E-01	APJYDQYYACXCRM-UHFFFAOYSA-N
279	R-ZHP	Uracil	1 (0.85,1.18)	1.11 (0.97,1.34)	0.77 (0.69,0.9)	0.65 (0.55,0.81)	1.30E-07	2.15E-07	5.36E-01	1.45E-02	8.31E-04	ISAKRJDGNUQOIC-UHFFFAOYSA-N
280	R-ZHN	Xylose	1 (0.78,1.27)	0.94 (0.74,1.14)	1.08 (0.87,1.26)	1.35 (1.04,1.83)	1.24E-02	7.13E-03	8.27E-01	6.58E-01	1.01E-01	SRBFZHDQGSBBOR-IOVATXLUSA-N

TABLE E3. 105 metabolites associated with OCS treatment.

Idx	Method	Metabolites	p-value	FDR	INCHIKEY
1	ZHP	Sulfamethoxazole	5.31E-02	4.30E-02	JLKIGFTWXXRPMT-UHFFFAOYSA-N
2	ZHP	Salicyluric acid	2.78E-05	1.36E-04	ONJSZLXSECQROL-UHFFFAOYSA-N
3	ZHP	Acetaminophen	3.84E-02	3.33E-02	RZVAJINKPMORJF-UHFFFAOYSA-N
4	ZHP	2-Furoylglycine	8.71E-04	2.27E-03	KSPQDMRTZZYQLM-UHFFFAOYSA-N
5	ZHP	3-Indoleacrylic acid	2.89E-03	5.12E-03	PLVPPLCLBIEYEA-AATRIKPKSA-N
6	ZHP	4-Acetamidobutanoic acid	5.57E-03	8.14E-03	UZTFMUBKZQVKLK-UHFFFAOYSA-N
7	ZHP	Ferulic acid	7.42E-05	2.94E-04	KSEBMYQBYZTDHS-HWKANZROSA-N
8	ZHP	Pantothenic acid	4.86E-05	2.03E-04	GHOKWGTUZJEAQD-ZETCQYMHSA-N
9	ZHP	Valeryl-carnitine (C5:0)	2.43E-02	2.50E-02	VSNFQQXVMPSASB-SNVBAGLBSA-N
10	ZHP	Nicotinamide	1.08E-02	1.32E-02	DFPAKSUCGFBDDF-UHFFFAOYSA-N
11	ZHP	1,3-Dimethyluric acid	4.07E-02	3.43E-02	OTSBKHHWSQYEHK-UHFFFAOYSA-N
12	ZHP	Kynurenic acid	2.70E-03	5.00E-03	HCZHHEIFKROPDY-UHFFFAOYSA-N
13	ZHP	Nicotinuric acid	2.85E-03	5.16E-03	ZBSGKPYXQINNGF-UHFFFAOYSA-N
14	ZHP	4-Pyridoxic acid	1.87E-02	1.97E-02	HXACOUQIXZGNBF-UHFFFAOYSA-N
15	ZHP	Xanthine	7.42E-03	9.66E-03	LRFVTYWOQMYALW-UHFFFAOYSA-N
16	ZHP	2,3-Dihydroxypyridine	2.99E-03	5.09E-03	GGOZGYRTNQBSSA-UHFFFAOYSA-N
17	ZHP	1-Methyluric acid	6.11E-03	8.35E-03	QFDRTQONISXGJA-UHFFFAOYSA-N
18	ZHP	5-S-Methylthioadenosine	3.56E-02	3.22E-02	WUUGFSXJNOTRMR-IOSLPCCCSA-N
19	ZHP	Acetaminophen glucuronide	1.77E-03	3.88E-03	IPROLSVTVHAQLE-BYNIDDHOSA-N
20	ZHP	Cyclohexylamine	4.13E-03	6.62E-03	PAFZNILMFXTMIY-UHFFFAOYSA-N
21	ZHP	Homarine	3.04E-02	2.81E-02	BRTLKRNVNFIOPJ-UHFFFAOYSA-N
22	ZHP	Amoxicillin	1.28E-03	2.96E-03	LSQZJLSUYDQPKJ-NJBDSQKTSA-N
23	ZHP	Tryptophan	2.45E-04	8.17E-04	QIVBCDIJIAJPQS-VIFPVBQESA-N
24	ZHP	N-Acetylneuraminic acid	1.86E-02	2.01E-02	SQVRNKJHWKZAKO-PFQGKNLYSA-N
25	ZHP	N6-Acetyl-lysine	2.56E-02	2.54E-02	DTERQYGMUDWYAZ-ZETCQYMHSA-N
26	ZHP	N2-Acetyl-histidine	2.02E-04	7.01E-04	KBOJOGQFRVVWBH-ZETCQYMHSA-N
27	ZHP	1-Methylnicotinamide	8.64E-09	5.14E-08	LDHMAVIPBRSVRG-UHFFFAOYSA-O
28	ZHP	Proline-Hydroxyproline	3.35E-02	3.07E-02	ONPXCLZMBSJLSP-CSMHCCOUSA-N
29	ZHP	Glycocyamine	6.01E-03	8.35E-03	BPMFZUMJYQTVII-UHFFFAOYSA-N
30	ZHP	N-Acetylputrescine	1.16E-02	1.38E-02	KLZGKIDSEJWEDW-UHFFFAOYSA-N
31	ZHP	Cystathionine	4.43E-03	6.84E-03	ILRYLPWNYFXEMH-WHFBIAKZSA-N
32	ZHP	Glucosamine	2.47E-03	4.68E-03	MSWZFWKMSRAUBD-IVMDWMLBSA-N
33	ZHP	Arginine	5.25E-02	4.29E-02	ODKSFYDXXFIFQN-BYPYZUCNSA-N
34	ZHP	Histidine	1.67E-02	1.83E-02	HNDVDQJCIGZPNO-YFKPBYRVSA-N
35	ZHP	Homoarginine	3.79E-08	2.11E-07	QUOGESRFPZDMMT-YFKPBYRVSA-N
36	ZHP	N,N,N-Trimethyl-lysine	3.19E-04	9.49E-04	MXNRLFUSFKVQSK-QMMMGPOBSA-N
37	ZHP	2-Aminobenzoic acid	2.89E-02	2.74E-02	RWZYAGGXGHYGMB-UHFFFAOYSA-N
38	ZHP	Acetyl-cysteine	1.86E-02	1.99E-02	PWKSKIMOESPYIA-BYPYZUCNSA-N
39	ZHP	Cortisol	1.90E-34	1.58E-32	JYGXADMDTFJGBT-VWUMJDOOSA-N
40	ZHP	Hexaethylene glycol	3.04E-05	1.41E-04	IIRDTKBZINWQAW-UHFFFAOYSA-N
41	ZHP	N-Acetyl-tyrosine	1.61E-03	3.63E-03	CAHKINHBCWCHCF-JTQLQIEISA-N
42	ZHP	N-Acetyl-threonine	4.05E-02	3.44E-02	PEDXUVCGOLSNLQ-WUJLRWPWSA-N

Idx	Method	Metabolites	p-value	FDR	INCHIKEY
43	ZHP	Omeprazole	3.15E-04	9.72E-04	SUBDBMMJDZJVOS-UHFFFAOYSA-N
44	ZHP	Isoleucine	2.43E-02	2.47E-02	AGPKZVBTJJNPAG-WHFBIAKZSA-N
45	ZHP	Salbutamol	1.58E-02	1.80E-02	NDAUXUAQIAJITI-UHFFFAOYSA-N
46	ZHP	Pyrrolidine	7.19E-04	2.07E-03	RWRDLPDLKQPQOW-UHFFFAOYSA-N
47	ZHP	Betonicine	3.98E-02	3.42E-02	MUNWAHDYFVYIKH-RITPCOANSA-N
48	ZHP	Sucrose (disaccharide)	1.10E-04	4.17E-04	CZMRCDWAGMRECN-UGDNZRGBSA-N
49	ZHP	Ethanolamine	3.70E-02	3.25E-02	HZAXFHJVJLSVMW-UHFFFAOYSA-N
50	ZHP	Ornithine	4.62E-02	3.81E-02	AHLPHDHHMVZTML-UHFFFAOYSA-N
51	ZHP	Cortisone metabolite	4.38E-34	1.83E-32	MFYSYFVPBJMHGN-ZPOLXVRWSA-N
52	ZHP	Dihydrocortisol	3.57E-18	7.44E-17	
53	ZHP	Dihydrotestosterone metabolite 1	2.00E-11	1.52E-10	
54	ZHP	Dihydrotestosterone metabolite 2	2.71E-10	1.88E-09	
55	ZHP	Decadienoyl-carnitine (C10:2)	1.87E-02	1.95E-02	
56	ZHP	Decatrienoyl-carnitine (C10:3)	4.30E-02	3.58E-02	
57	ZHP	5-Hydroxyomeprazole	5.45E-02	4.33E-02	
58	ZHP	Hydroxyhexanoyl-carnitine (C6:0-OH) 1	1.65E-02	1.83E-02	
59	ZHP	Isobar of Glutaryl-carnitine (C5:0-OOH)	6.60E-03	8.73E-03	
60	ZHP	Nitrophenylalanine	8.39E-03	1.06E-02	
61	ZHP	Acetaminophen metabolite	1.62E-02	1.82E-02	
62	ZHP	Salbutamol metabolite1	5.80E-03	8.33E-03	
63	ZHP	Prednisone metabolite 2	6.21E-17	7.39E-16	
64	ZHP	Thiophanate-methyl	4.97E-03	7.40E-03	
65	ZHP	Malonyl-carnitine (C2:0-OOH)	3.58E-02	3.21E-02	
66	ZHP	Hydroxypropionyl-carnitine (C3:0-OH)	9.77E-04	2.39E-03	
67	ZHP	Sulfamethoxazole metabolite	1.24E-02	1.46E-02	
68	ZHN	Hypoxanthine	1.12E-02	1.35E-02	FDGQSTZJBFJUBT-UHFFFAOYSA-N
69	ZHN	Xanthine	1.89E-04	6.85E-04	LRFVTYWOQMYALW-UHFFFAOYSA-N
70	ZHN	Kynurenic acid	8.89E-04	2.24E-03	HCZHHEIFKROPDY-UHFFFAOYSA-N
71	ZHN	Threonine	2.43E-02	2.44E-02	AYFVYJQAPQTCCC-GBXIJSLDSA-N
72	ZHN	Methylxanthine	5.37E-02	4.30E-02	MVOYJPOZRLFTCP-UHFFFAOYSA-N
73	ZHN	N-Acetylcarnosine	2.04E-03	4.15E-03	BKAYIFDRRZZKNF-SECBINFHSA-N
74	ZHN	Histidine	1.55E-02	1.79E-02	HNDVDQJCIGZPNO-YFKPBYRVSA-N
75	ZHN	Mannitol	2.42E-03	4.69E-03	FBPFZTCFMRRESA-KVTDHHQDSA-N
76	ZHN	Glucose	2.90E-03	5.03E-03	WQZGKKKJIJFFOK-DVKNGEFBSA-N
77	ZHN	Dideoxy-imino-ribitol	9.12E-03	1.13E-02	
78	ZHN	Testosterone glucuronide	3.38E-16	3.52E-15	
79	ZHN	Androstanediol glucuronide	1.85E-03	3.95E-03	
80	ZHN	Hydroxyandrosterone glucuronide	5.38E-17	7.47E-16	

Idx	Method	Metabolites	p-value	FDR	INCHIKEY
81	ZHN	Hydroxyandrostane glucuronide	3.96E-09	2.54E-08	
82	ZHN	Pregnanediol glucuronide	3.70E-14	3.08E-13	
83	ZHN	Nitrophenylalanine	8.35E-03	1.07E-02	
84	ZHN	Ethyl-glucuronide 2	2.37E-05	1.23E-04	
85	ZHN	Ethyl-glucuronide 1	2.86E-04	9.17E-04	
86	ZHN	Salbutamol sulfate	2.88E-02	2.76E-02	
87	ZHN	Cortisone	1.34E-15	1.24E-14	
88	ZHN	Dehydroepiandrosterone sulfate	3.95E-18	6.58E-17	
89	ZHN	Estrone glucuronide	2.47E-20	6.86E-19	
90	ZHN	Uric acid	7.70E-04	2.14E-03	
91	ZHN	Pseudouridine	1.03E-03	2.45E-03	
92	R-ZHP	5-Aminolevulinic acid	3.57E-03	5.95E-03	ZGXJTSGNIOSYLO-UHFFFAOYSA-N
93	R-ZHP	Alanine	2.64E-02	2.59E-02	QNAYBMKLOCPYGJ-REOHCLBHSA-N
94	R-ZHP	Allantoin	6.33E-03	8.51E-03	POJWUDADGALRAB-UHFFFAOYSA-N
95	R-ZHP	Aminovaleric acid	5.97E-03	8.43E-03	JJMDCOVWQOJGCB-UHFFFAOYSA-N
96	R-ZHP	Aspartic acid	1.85E-03	3.85E-03	CKLJMWTZIZZHCS-REOHCLBHSA-N
97	R-ZHP	Biopterin	2.84E-02	2.75E-02	LHQIJBMDNUYRAM-DZSWIPIPSA-N
98	R-ZHN	Maltose	4.15E-03	6.53E-03	GUBGYTABKSRVRQ-DKBJLJRDSA-N
99	R-ZHN	N-Methyl-D-aspartic acid	4.20E-05	1.84E-04	HOKKHZGPKSLGJE-GSVOUGTGSA-N
100	R-ZHN	O-Acetylserine	3.63E-02	3.22E-02	VZXPDPZARILFQX-BYPYZUCNSA-N
101	R-ZHP	Pyroglutamylglycine	2.12E-03	4.21E-03	MGEFGYONNZYSPY-UHFFFAOYSA-N
102	R-ZHP	S-Adenosylhomocysteine	3.02E-02	2.83E-02	ZJUKTBDSGOFHSH-WFMPWKQPSA-N
103	R-ZHP	Sarcosine	3.75E-03	6.13E-03	FSYKKLYZXJSNPZ-UHFFFAOYSA-N
104	R-ZHP	Uracil	8.47E-04	2.28E-03	ISAKRJDGNUQOIC-UHFFFAOYSA-N
105	R-ZHN	Xylose	4.76E-03	7.21E-03	SRBFZHDQGSBBOR-IOVATXLUSA-N

TABLE E4. Unbalanced metabolites in training/validation split.

Idx	Method	Metabolites	p value	INCHIKEY
1	ZHP	Adenosine	0.04	OIRDTQYFTABQOQ-KQYNXXCUSA-N
2	ZHP	N,N-Dimethyl-lysine	0.03	XXEWFEBMSGLYBY-ZETCQYMHSA-N
3	ZHP	Nonanoyl-carnitine (C9:0)	0.03	
4	ZHP	Hexenoyl-carnitine (C6:1)	0.03	
5	ZHN	Threonine	0.004	AYFVYJQAPQTCCC-GBXIJSLDSA-N
6	ZHN	Glucose	0.05	WQZGKKKJIJFFOK-DVKNGEFBSA-N
7	ZHN	Galacturonic acid	0.02	AEMOLEFTQBMNLQ-WAXACMCWSA-N
8	R-ZHN	Galacturonic acid	0.01	IAJILQKETJEXLJ-RSJOWCBRSA-N
9	R-ZHP	Pyroglutamylglycine	0.04	MGEFGYONNZYSPY-UHFFFAOYSA-N

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