Supplemental Data 1. Methodological considerations and validation of results.

Content:

1. Extended discussion of the strengths and limitations of the study:

While untargeted metabolomics can provide valuable input for hypothesis generation, care should be taken in the biological interpretation at single metabolite level, as compound detection is less accurate compared to targeted high-confidence workflows (1). For instance, we found that the amino acid effects generally trended in coherence with our previously reported targeted data in a larger ME/CFS cohort (2), but deviations were seen for several sulphur-containing amino acid metabolites. Further, factors such as variable storage time and compound stability may affect the data quality (2). The samples of the present study were collected in 2015-2017 and there may be variable metabolite decay, but control data analysis did not indicate that differences in storage time had major influence on the main findings (data not shown). The sample size is relatively small, although this is the largest broad-spectrum metabolomics study so far reported in the ME/CFS patients. The limitations of a small sample size were to some extent compensated by the large amount of data for each subject. For example, the effects on some parameters were validated with different technologies, and multifaceted cross-evaluation returned adequate support for the suggested metabotypes.

The data were preprocessed using conventional procedures, before we identified significantly different metabolites in ME/CFS patients compared to healthy subjects and clustered subjects with similar patterns of metabolite concentration shifts. We decided upon an exploratory strategy for our data analysis, and therefore applied t test statistics as filter method to select relevant features for multivariate statistics. This approach is known to be susceptible for overfitting the PCA results, so the results should be interpreted with caution. We addressed this potential bias by performing a PCA on all 610 metabolites within the dataset, which revealed that the proposed metabotypes are still highly relevant for explaining the observed variance within both sexes for the entire dataset (Section 2, below). We concluded that our EDA strategy returned statistically and biologically meaningful results, supported by patient data, lipidomics data and supplementary laboratory data. The three ME/CFS subsets with different metabotypes emerged when we focused on compounds of known identity (excluding molecules that were only partially characterized and xenobiotic substances). Although we cannot exclude some influence, the subsets were not explained by differences in age, sex, dietary supplements and medication (Sections 3-5, below). Neither did we find that fasting state influenced the ME/CFS subsets, supporting the use of non-fasting blood draws as recently recommended for metabolic profiling (3, 4).

Previous broad-spectrum metabolomics studies primarily aimed to find potential biomarkers, and therefore identified metabolites with the highest statistical probability to predict ME/CFS (5-9). Since our aim was to gain broad insight into pathways that might be involved, we used a relatively low stringency level for statistical significance when comparing single molecule concentrations in ME/CFS patient and HC subjects ($p<0.05$). Such differences in study design, as well as differences in analytical technologies and cohort size and patient characteristics, represent plausible reasons why the statistically significant metabolites differ somewhat between the various studies. In addition, the presence of different metabolic phenotypes may explain why the effects vary more for some metabolites than others within the ME/CFS group, and when comparing different cohorts and studies. For example, our findings may indicate that BMI influences context-dependent metabolic adaptations. Notably, we found that the two main ME/CFS metabotype subsets sometimes expressed opposing effects, and this neutralized the potential effect on group level for some metabolites.

2. Possible impact of statistical method

Missing imputation method: We excluded metabolites with more than 25% missing values and applied the half-minimum (HM) method for imputation. To evaluate the possible skewed impact of missing value imputation, we performed Fischers and Chi-squared analyses between different groups (ME vs HC, sex, metabotype) (Supplemental Data Set 3). This indicated that around 2 – 7% of the 610 metabolites had non-random distribution of missing values depending on the type of comparison being done. For the 159 significant variables from the univariate analyses, there was a similar percentage of metabolites displaying a non-random distribution of missing values. These results confirm that missing values imputations had negligible impact on the overall results in the multivariate analyses.

Filter method: The K-means algorithm that we applied for EDA purposes does not incorporate a feature selection method when applied outside a wrapper/embedded ML model, so a meaningful result depends on a feature selection step in advance. We used t-test statistics as filter method for our feature selection step, providing the 159 variables used for multivariate analyses. To evaluate if this cased overfitting of the results, we performed PCA on all 610 variables. The PCA on all 610 metabolites with an overlay of the proposed metabotypes (Figure 1 below) reproduced the influence of metabotypes in the total cohort, as well as in female and male separately. This supported that the choice of filter method returned adequate data, but the limitations of univariate feature selection for the purpose of clustering and identifying patient subtypes in high dimensional datasets is well known issue in the statistical community (10, 11). The variable selection approach applied in this study could potentially exclude subtle discriminating features that display a stronger joint effect with other related variables, and there are also apparent drawbacks in identifying exact number of patient subtypes with conventional clustering methods as these methods could introduce a potential bias from the investigator, and techniques to identify an exact number of clusters display between-method variation in the estimation of k.

The statistical method was supported by biologically relevant results. The different metabolic profiles found in the ME/CFS patient subsets were validated by multiple independent measurements. Further, the findings were consistent with expected effects of relevant biological contexts, based on available literature.

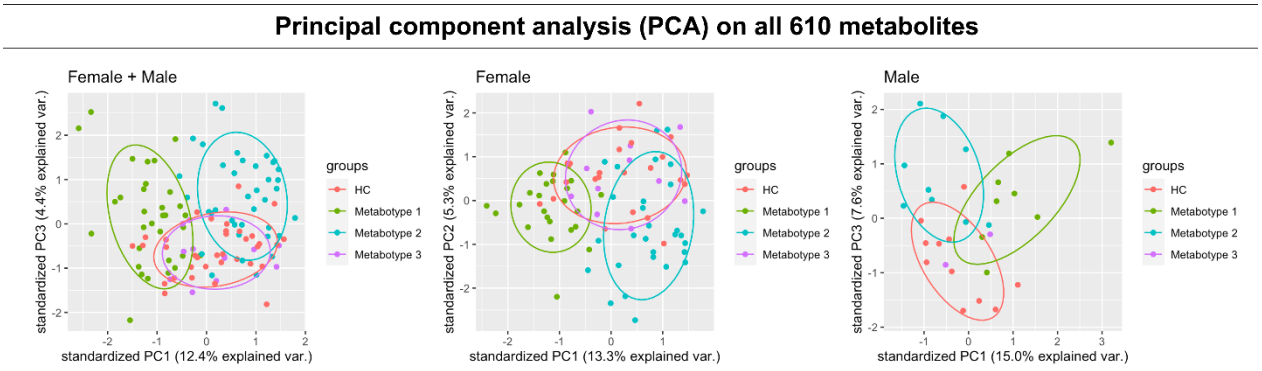

Figure 1: PCA with metaobtype overlay, based on 610 metabolites.

3. Possible impact of sex:

The possible influence of sex on the clustering results was evaluated at several levels. First, there was no significant difference in sex composition between 1) the overall HC and ME/CFS groups (Fischer's exact test; Table 1 in the article), or 2) the HC group and the ME/CFS metabotype subsets (ME-M1, ME-M2 and ME-M3) (Chi squared test and Fischer's exact test; Table 1 in the article). Next, separate multivariate analyses using the 159 significant metabolites from the original univariate analysis confirmed that the K-means clustering patterns were largely maintained in both male and female subsets compared to mixed group (Figure 2 below). Further, the metabotypes represented different subsets in both female and male in separate PCA plots, when overlaying the original metabotype annotations (Figure 2 below). We also performed separate univariate comparison of the metabolomics data (Supplemental Data Set 4) and laboratory analyses (Supplemental Data 2) in female and male. Our conclusion is that the presented ME/CFS metabotypes are not driven by sex, and are adequately expressed in both female and male.

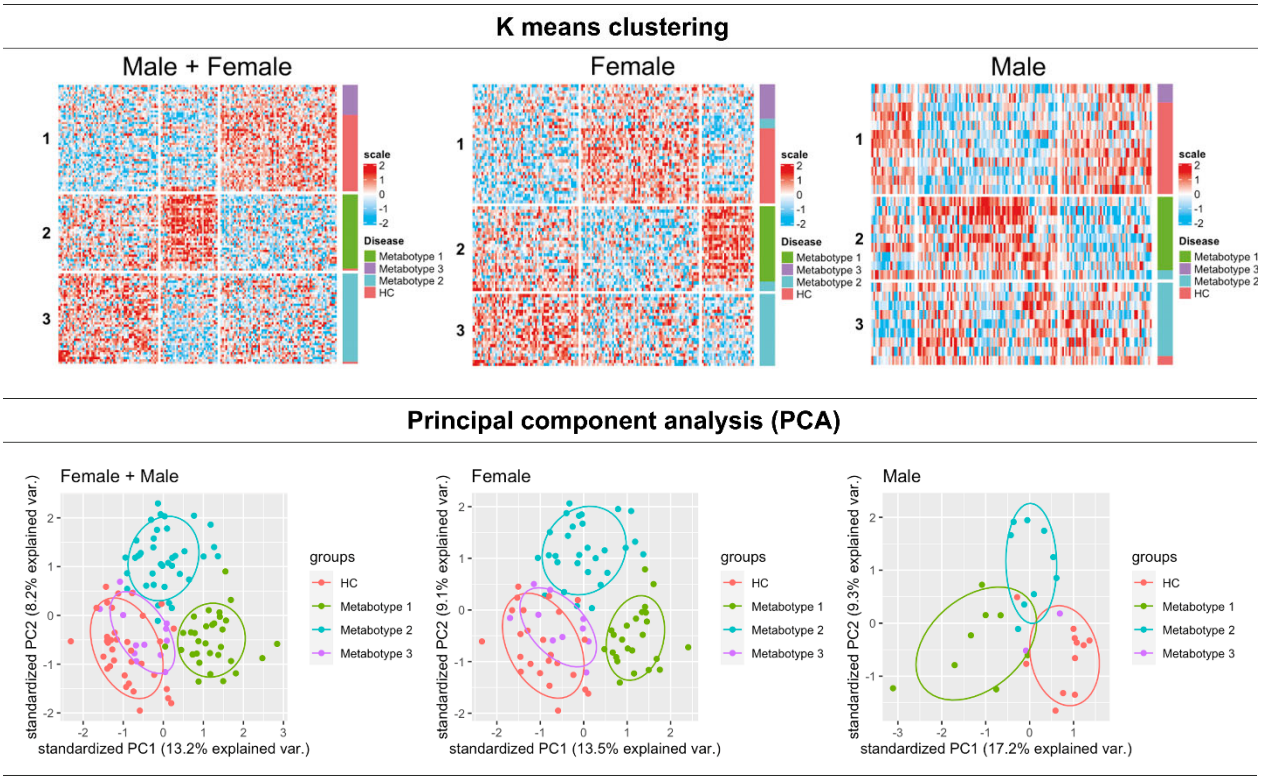

Figure 2: K-means clustering and PCA in ME/CFS and HC according to sex.

4. Possible impact of BMI

There was no significant difference in mean BMI between the HC and ME/CFS groups. However, mean BMI was significantly higher in the ME-M2 patients compared to the ME-M1 patients (25.7 vs 23.1) (Table 1 in the article). In order to perform categorical testing we divided the patients with BMI < 25 (n=48) and BMI > 25 (n=35), and found that ME-M2 had significantly higher proportion of subjects with BMI > 25 compared to HC (Fischer's exact test, $p<0.05$). To evaluate the influence of BMI on the results of the multivariate analysis, Pearson correlation analysis was performed between BMI and the principal components of the PCA (Figure 3, below). There was a significant, yet weak, association between BMI and PC2 ($r = 0.32$, $R^2 = 0.102$, $P < 0.05$). To further investigate if the results were driven by high BMI, K-means clustering and PCA were repeated after exclusion of subjects with BMI > 25 (Figure 4, below). This was performed both on group level, and separately on female and male. The results were largely consistent with the findings in the total cohort, and when dividing by sex. Hence, although we cannot exclude the possibility that there is some influence of BMI, our evaluation concludes that BMI is unlikely to be a primary determinant of the observed patterns.

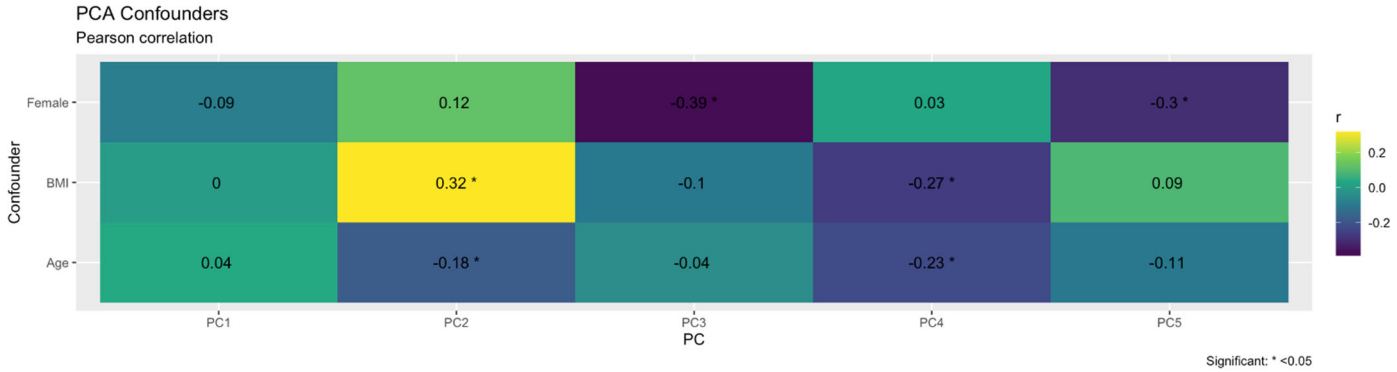

Figure 3: Pearson correlation analysis between BMI and the principal components of the PCA

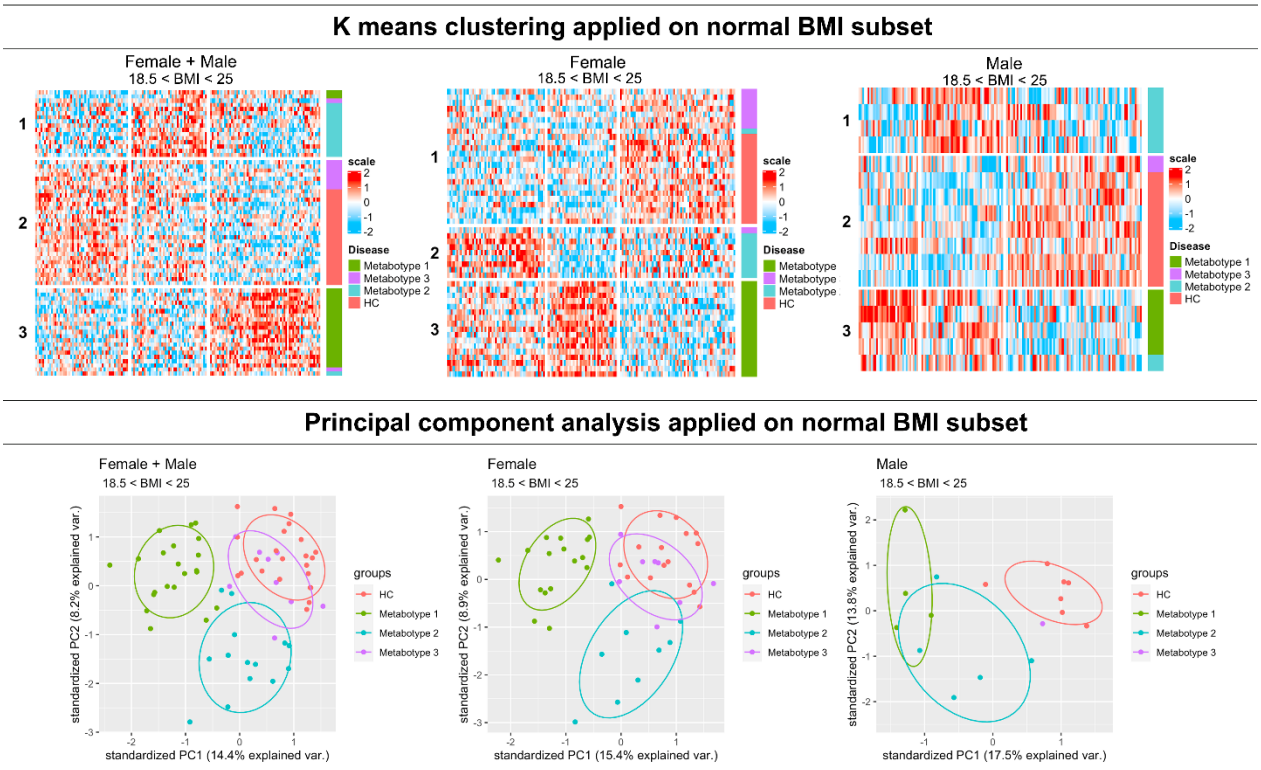

Figure 4: K-means clustering and PCA in ME/CFS and HC excluding subject with BMI>25.

5. Possible impact of fasting, diet and drugs

Fasting: The 12 patients that performed overnight fasting before sampling distributed randomly between the three subsets (Table 1 in the article). This supports that fasting state has minor influence on the proposed ME/CFS metabotypes.

Diett and drugs: To evaluate if the suggested metabotypes associated with systematic differences in diet and medication, we took advantage of the data of 185 xenobiotic molecules that were available in the global metabolomics dataset (Supplemental Data Set 1, sheet 11). To assess the use of specific drug classes, we counted the subjects having detectable levels of the associated drug derivatives. If a drug had several metabolites, we used the respective metabolite with the highest occurrence (Drug Table 1, below). The drug metabolite data was also compared with the drugs documented in the patient journal (Drug Table 2, below). As expected, the findings generally agreed with larger consumption of supportive drugs in ME/CFS patients relative to the HC group. However, the data indicated no significant differences in drug use between the ME/CFS metabotype subsets regarding analgesics, gastro-esophagal-reflux drugs, allergy medication and anti-epileptics. Yet, it appears that our strategy based on drug metabolites may have overestimated the number of users of certain drugs. For instance, metoprolol (or its metabolites) was detected in 22.9% of the patients and 8.6% of the HC subjects, whereas the number of patients that had metoprolol documented in their medical files was only 3.6%. Further, paracetamol derivatives were detected in 84.4% and 84.2% for ME-m1 and ME-m2 respectively, and in 97.1% of the HC group. For all other analgesics there were proportionally fewer observations in the HC group. Zolpidem (a sedative/hypnotic drug used for anxiety/sleep) was detected in a larger proportion of ME-m2 patient (15.8%) compared to ME-m1 (3.1%), but this was not statistically significant due to few observations.

Evaluation of xenobiotic compounds originating from foods revealed lower levels of metabolites related to peppers (such as piperin and 2-piperidinone) and caffeine in ME/CFS patients compared to HC subjects (Figure 4, below). There were also lower levels of a metabolite related to consumption of cereal and milk products (methyl glucopyranoside) in the patients. The general tendency of low dietary xenobiotics levels may agree with a low total dietary load, as would agree with limited caloric expenditure due to the debilitating condition. Of importance for the present study, the dietary xenobiotics patterns were similar among the ME-M1 and ME-M2 subsets, minimizing the probability that a systematic difference in xenobiotics causes the observed metabolic phenotypes.

Drug Table 1: Drugs detected by the HD4 platform. Compounds identified as drugs or drug metabolites by the global metabolomics platform where used to determined the number of patients or controls positive for each drug detected in the dataset. For each drug, either the drug itself or the drug metabolite with the highest number of positive observations were counted.

	HC		ME/CFS		m1		m2		m3	
	N	%	N	%	N	%	N	%	N	%
GASTRIC										
RANITIDINE	1	2.86	1	1.20	1	3.13	0	0.00	0	0.00
OMEPRAZOLE	0	0.00	3	3.61	1	3.13	2	5.26	0	0.00
PANTOPRAZOLE	1	2.86	2	2.41	1	3.13	1	2.63	0	0.00
LANSOPRAZOLE	1	2.86	3	3.61	1	3.13	2	5.26	0	0.00
ANALGESICS										
IBUPROFEN	3	8.57	22	26.51	8	25.00	10	26.32	4	30.77
NAPROXEN	1	2.86	6	7.23	3	9.38	2	5.26	1	7.69
TRAMADOL	1	2.86	11	13.25	5	15.63	6	15.79	0	0.00
PARACETAMOL	34	97.14	71	85.54	27	84.38	32	84.21	12	92.31
ASTHMA/ALLERGY										
SALMETEROL	1	2.86	1	1.20	1	3.13	0	0.00	0	0.00
CETIRIZINE	0	0.00	7	8.43	3	9.38	3	7.89	1	7.69
CARDIOVASCULAR										
METOPROLOL	3	8.57	19	22.89	9	28.13	7	18.42	3	23.08
ANTIEPILEPTICS										
LAMOTRIGINE	0	0.00	2	2.41	1	3.13	1	2.63	0	0.00
GABAPENTIN	0	0.00	2	2.41	1	3.13	1	2.63	0	0.00
SEDATIVES										
ZOLPIDEM	0	0.00	7	8.43	1	3.13	6	15.79	0	0.00
ANTIDEPRESSANTS										
MAPROTILINE	0	0.00	5	6.02	3	9.38	1	2.63	1	7.69
SERTRALINE	0	0.00	2	2.41	0	0.00	1	2.63	1	7.69
MIRTAZAPINE	0	0.00	1	1.20	0	0.00	0	0.00	1	7.69
STIMULANTS										
METHYLPHENIDATE	0	0.00	1	1.20	0	0.00	1	2.63	0	0.00
THESE DRUG METABOLITES SHOWED SIGNIFICANT DISCREPANCY WITH DRUG PRESCRIPTIONS AND PRESUMABLY HAVE OTHER ORIGIN:										
WARFARIN	29	82.86	62	74.70	22	68.75	29	76.32	11	84.62
CARBOCISTEINE	35	100.00	76	91.57	30	93.75	35	92.11	11	84.62
HYDROQUINONE	35	100.00	83	100.00	32	100.00	38	100.00	13	100.00

Drug Table 2: Drugs documented in the patient Journal. The drugs documented in patient journals were identified by their ATC codes and counted.

		ME/CFS		m1		m2		m3	
DRUG	**ATC**	**N(74)**	**%**	**N(28)**	**%**	**N(38)**	**%**	**N(8)**	**%**
DIGESTIVE TRACT									
GASTRO-ESOPHAGAL-REFLUX DISEASE (TOTAL)	A02B	11	14.86	6	21.43	4	10.53	1	12.50
RANITIDINE	A02BA02	1	1.35	1	3.57	0	0.00	0	0.00
PANTOPRAZOLE	A02BC02	4	5.41	2	7.14	2	5.26	0	0.00
LANSOPRAZOLE	A02BC03	1	1.35	0	0.00	0	0.00	1	12.50
ESOMEPRAZOLE	A02BC05	5	6.76	3	10.71	2	5.26	0	0.00
ANTIEMETIC/NAUSEA	A03F/A04A								
METOCLOPRAMIDE	A03FA01	2	2.70	1	3.57	1	2.63	0	0.00
ONDANSETRON	A04AA01	1	1.35	1	3.57	0	0.00	0	0.00
CONSTIPATION	A06A								
LACTULOSE	A06AD11	1	1.35	0	0.00	1	2.63	0	0.00
MACROGOL, COMBINATIONS	A06AD65	1	1.35	1	3.57	0	0.00	0	0.00
INTESTINAL ANTIINFLAMMATORY	A07E								
MESALAZINE	A07EC02	2	2.70	2	7.14	0	0.00	0	0.00
BALSALAZIDE	A07EC04	1	1.35	1	3.57	0	0.00	0	0.00
SUPPLEMENTS									
MULTIVITAMINS	A11BA	13	17.57	4	14.29	8	21.05	1	12.50
VITAMIN D AND A + COMBINATIONS	A11CC	11	14.86	5	17.86	6	15.79	0	0.00
VITAMIN B1 + INCLUDING B6 AND B12	A11D	2	2.70	0	0.00	2	5.26	0	0.00
VITAMIN B-COMPLEX + INCL. COMBINATIONS	A11EA	3	4.05	2	7.14	1	2.63	0	0.00
VITAMIN C	A11GA	5	6.76	2	7.14	3	7.89	0	0.00
									0.00
VITAMIN B12 AND FOLIC ACID (USPECIFIED)	B03B	2	2.70	1	3.57	1	2.63	0	0.00
CYANOCOBALAMIN	B03BA01	2	2.70	1	3.57	1	2.63	0	0.00
HYDROXOCOBALAMIN	B03BA03	5	6.76	2	7.14	3	7.89	0	0.00
FOLIC ACID	B03BB01	1	1.35	0	0.00	1	2.63	0	0.00
CALCIUM	A12AX	3	4.05	1	3.57	2	5.26	0	0.00
POTASSIUM	A12B	1	1.35	1	3.57	0	0.00	0	0.00
IRON PREPARATIONS	B03A	4	5.41	1	3.57	2	5.26	1	12.50
MAGNESIUM (DIFFERENT SALTS IN COMBINATION)	A12CC30	8	10.81	2	7.14	5	13.16	1	12.50
OTHER MINERAL SUPPLEMENTS	A12C	4	5.41	1	3.57	3	7.89	0	0.00
HORMONAL THERAPIES									

HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE (TOTAL)	G03A	17	22.97	6	21.43	9	23.68	2	25.00
UNSPECIFIED	G03A	1	1.35	1	3.57	0	0.00	0	0.00
LEVONORGESTREL AND ETHINYLESTRADIOL	G03AA07	3	4.05	0	0.00	2	5.26	1	12.50
DESOGESTREL AND ETHINYLESTRADIOL	G03AA09	4	5.41	2	7.14	2	5.26	0	0.00
DROSPIRENONE AND ETHINYLESTRADIOL	G03AA12	4	5.41	0	0.00	4	10.53	0	0.00
MEDROXYPROGESTERONE	G03AC06	1	1.35	1	3.57	0	0.00	0	0.00
ETONOGESTREL	G03AC08	1	1.35	1	3.57	0	0.00	0	0.00
DESOGESTREL	G03AC09	3	4.05	1	3.57	1	2.63	1	12.50
LOCAL									
PLASTIC IUD WITH PROGESTERONE	G02BA03	1	1.35	1	3.57	0	0.00	0	0.00
OTHER SYSTEMIC FEMALE SEX HORMONE (TOTAL)	G03	5	6.76	3	10.71	2	5.26	0	0.00
ESTRADIOL	G03CA03	1	1.35	1	3.57	0	0.00	0	0.00
ESTRIOL	G03CA04	1	1.35	1	3.57	0	0.00	0	0.00
NORETHISTERONE AND ESTROGEN	G03FA01	1	1.35	1	3.57	0	0.00	0	0.00
CYPROTERONE AND ESTROGEN	G03HB01	2	2.70	0	0.00	2	5.26	0	0.00
THYROID PREPARATIONS (TOTAL)	H03A	5	6.76	2	7.14	3	7.89	0	0.00
LEVOTHYROXINE SODIUM	H03AA01	3	4.05	2	7.14	1	2.63	0	0.00
LIOTHYRONINE SODIUM	H03AA02	1	1.35	0	0.00	1	2.63	0	0.00
THYROID GLAND PREPARATIONS	H03AA05	1	1.35	0	0.00	1	2.63	0	0.00
ANALGESICS AND ANTIPYRETICS									
NSAIDs SYSTEMIC	M01A								
DICLOFENAC	M01AB05	1	1.35	0	0.00	1	2.63	0	0.00
DICLOFENAC, COMBINATIONS	M01AB55	1	1.35	0	0.00	1	2.63	0	0.00
PIROXICAM	M01AC01	1	1.35	0	0.00	1	2.63	0	0.00
IBUPROFEN	M01AE01	25	33.78	8	28.57	12	31.58	5	62.50
NAPROXEN	M01AE02	3	4.05	1	3.57	2	5.26	0	0.00
KETOPROFEN	M01AE03	1	1.35	0	0.00	1	2.63	0	0.00
NAPROXEN AND ESOMEPRAZOLE	M01AE52	5	6.76	2	7.14	3	7.89	0	0.00
NSAIDs TOPICAL	M02A								
KETOPROFEN	M02AA10	1	1.35	0	0.00	1	2.63	0	0.00
DICLOFENAC	M02AA15	2	2.70	1	3.57	1	2.63	0	0.00
OPIOIDS	N02A								
BUPRENORPHINE	N02AE01	1	1.35	0	0.00	1	2.63	0	0.00
CODEIN (IN COMBINATION WITH PARACETAMOL)	N02AJ06	12	16.22	6	21.43	6	15.79	0	0.00
TRAMADOL	N02AX02	8	10.81	4	14.29	4	10.53	0	0.00
OTHER ANALEGESICS AND ANTIPYRETICS	N02B								
ACETYLSALICYLIC ACID	N02BA01	1	1.35	1	3.57	0	0.00	0	0.00
PHENAZONE, COMBINATIONS EXCL. PSYCHOLEPTICS	N02BB51	1	1.35	1	3.57	0	0.00	0	0.00
PARACETAMOL	N02BE01	29	39.19	11	39.29	15	39.47	3	37.50

ANTIMIGRAINE	N02C								
SUMATRIPTAN	N02CC01	7	9.46	1	3.57	5	13.16	1	12.50
ZOLMITRIPTAN	N02CC03	1	1.35	0	0.00	0	0.00	1	12.50
RIZATRIPTAN	N02CC04	4	5.41	1	3.57	2	5.26	1	12.50
ELETRIPTAN	N02CC06	1	1.35	0	0.00	0	0.00	1	12.50
CLONIDINE	N02CX02	3	4.05	1	3.57	2	5.26	0	0.00
CNS SUPPRESSIVE/STIMULATING DRUGS									
ANTIEPILEPTICS	N03A								
LAMOTRIGINE	N03AX09	1	1.35	0	0.00	1	2.63	0	0.00
GABAPENTIN	N03AX12	2	2.70	1	3.57	1	2.63	0	0.00
ANTIPSYCHOTICS/ANXIOLYTICS/HYPNOTICS/SEDATIVE	N05A/B/C								
QUETIAPINE	N05AH04	1	1.35	1	3.57	0	0.00	0	0.00
DIAZEPAM	N05BA01	1	1.35	1	3.57	0	0.00	0	0.00
OXAZEPAM	N05BA04	3	4.05	0	0.00	3	7.89	0	0.00
HYDROXYZINE	N05BB01	1	1.35	0	0.00	1	2.63	0	0.00
NITRAZEPAM	N05CD02	2	2.70	2	7.14	0	0.00	0	0.00
FLUNITRAZEPAM	N05CD03	1	1.35	1	3.57	0	0.00	0	0.00
ZOPICLONE	N05CF01	17	22.97	7	25.00	7	18.42	3	37.50
ZOLPIDEM	N05CF02	7	9.46	1	3.57	6	15.79	0	0.00
MELATONIN	N05CH01	17	22.97	13	46.43	3	7.89	1	12.50
ANTIDEPRESSANTS (TOTAL)	N06A	12	16.22	5	17.86	6	15.79	1	12.50
TRIMIPRAMINE	N06AA06	1	1.35	0	0.00	1	2.63	0	0.00
AMITRIPTYLINE	N06AA09	3	4.05	2	7.14	1	2.63	0	0.00
SERTRALINE	N06AB06	1	1.35	0	0.00	1	2.63	0	0.00
ESCITALOPRAM	N06AB10	3	4.05	1	3.57	2	5.26	0	0.00
OXITRIPTAN	N06AX01	1	1.35	1	3.57	0	0.00	0	0.00
MIANSERIN	N06AX03	3	4.05	1	3.57	1	2.63	1	12.50
OTHER									
METHYLPEHNIDATE	N06BA04	1	1.35	0	0.00	1	2.63	0	0.00
NALTREXONE	N07BB04	4	5.41	2	7.14	1	2.63	1	12.50
PRAMIPEXOLE	N04BC05	1	1.35	0	0.00	0	0.00	1	12.50
ALLERGY/ASTHMA									
DECONGESTANT NASAL PREPARATIONS FOR TOPICAL USE	R01A								
XYLOMETAZOLINE	R01AA07	1	1.35	1	3.57	0	0.00	0	0.00
LEVOCABASTINE	R01AC02	1	1.35	0	0.00	1	2.63	0	0.00
FLUTICASONE	R01AD08	2	2.70	0	0.00	1	2.63	1	12.50
MOMETASONE	R01AD09	7	9.46	2	7.14	4	10.53	1	12.50
TRIAMCINOLONE	R01AD11	1	1.35	1	3.57	0	0.00	0	0.00
FLUTICASONE FUROATE	R01AD12	3	4.05	2	7.14	1	2.63	0	0.00

PHENYLPROPANOLAMINE (NASAL DEGONCESTANT, SYSTEMIC)	R01BA01	2	2.70	0	0.00	2	5.26	0	0.00
INHALANTS FOR FOR OBSTRUCTIVE AIRWAY DISEASE	R03A/B								
SALBUTAMOL	R03AC02	6	8.11	2	7.14	3	7.89	1	12.50
SALMETEROL AND FLUTICASONE	R03AK06	2	2.70	2	7.14	0	0.00	0	0.00
FORMOTEROL AND BUDESONIDE	R03AK07	2	2.70	1	3.57	1	2.63	0	0.00
CICLESONIDE	R03BA08	1	1.35	0	0.00	1	2.63	0	0.00
DRUGS FOR SYSTEMIC USE, OBSTRUCTIVE AIRWAY DISEASE	R03C/D								
TERBUTALINE	R03CC03	1	1.35	1	3.57	1	2.63	0	0.00
THEOPHYLLINE	R03DA04	1	1.35	0	0.00	1	2.63	0	0.00
MONTELUKAST	R03DC03	1	1.35	0	0.00	1	2.63	0	0.00
ANTI-COUGH									
ETHYLMORPHINE	R05DA01	1	1.35	0	0.00	1	2.63	0	0.00
ANTIHISTAMINES FOR SYSTEMIC USE	R06A								
DEXCHLORPHENIRAMINE	R06AB02	1	1.35	0	0.00	1	2.63	0	0.00
ALIMEMAZINE	R06AD01	5	6.76	4	14.29	1	2.63	0	0.00
PROMETHAZINE	R06AD02	1	1.35	0	0.00	1	2.63	0	0.00
CETIRIZINE	R06AE07	7	9.46	4	14.29	3	7.89	0	0.00
LORATADINE	R06AX13	2	2.70	0	0.00	1	2.63	1	12.50
DESLORATADINE	R06AX27	8	10.81	4	14.29	3	7.89	1	12.50
DECONGESTANTS AND ANTIALLERGICS	S01G								
TETRYZOLINE, COMBINATIONS	S01GA52	1	1.35	0	0.00	1	2.63	0	0.00
CROMOGLICIC ACID	S01GX01	1	1.35	0	0.00	1	2.63	0	0.00
LEVOCABASTINE	S01GX02	3	4.05	0	0.00	3	7.89	0	0.00
KETOTIFEN	S01GX08	1	1.35	0	0.00	0	0.00	1	12.50
OTHER									
DIFFERENT CORTICOSTEROID PREPARATIONS									
TRIAMCINOLONE (SYSTEMIC CORTICOSTEROID)	H02AB08	1	1.35	1	3.57	0	0.00	0	0.00
TOPICAL CORTICOSTEROIDS (BETAMETHASONE)	D07A	3	4.05	1	3.57	1	2.63	1	12.50
TOPICAL CORTICOSTEROIDS (PREDNISOLONE)	C05AA04	1	1.35	0	0.00	0	0.00	1	12.50
CARDIAC DISEASE/HYPERTENSION	C0								
GLYCERYL TRINITRATE	C01DA02	1	1.35	1	3.57	0	0.00	0	0.00
FUROSEMIDE	C03CA01	2	2.70	1	3.57	1	2.63	0	0.00
METOPROLOL	C07AB02	3	4.05	3	10.71	0	0.00	0	0.00
LERCANIDIPINE	C08CA13	1	1.35	1	3.57	0	0.00	0	0.00
ATORVASTATIN	C10AA05	1	1.35	1	3.57	0	0.00	0	0.00
EZETIMIBE	C10AX09	1	1.35	1	3.57	0	0.00	0	0.00
ANTIBIOTICS/ANTIINFECTIVES									
MECILLINAM	J01CA11	1	1.35	0	0.00	1	2.63	0	0.00
METHENAMINE	J01XX05	1	1.35	0	0.00	1	2.63	0	0.00

CHLORAMPHENICOL	S01AA01	2	2.70	0	0.00	2	5.26	0	0.00
ANTIGOUT									
ALLOPURINOL	M04AA01	1	1.35	1	3.57	0	0.00	0	0.00

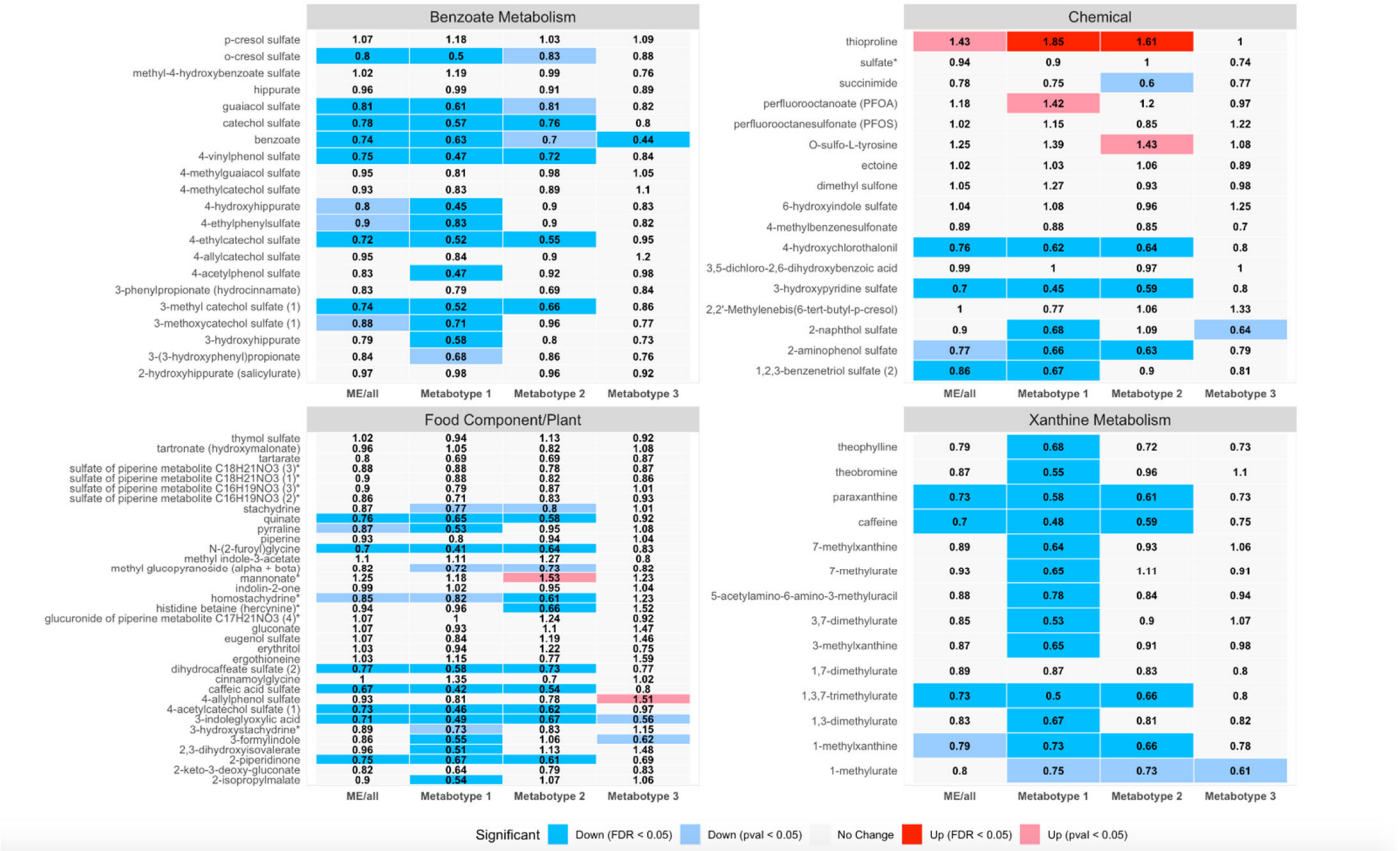

Figure 4: Food components: Heatmap with fold change values relative to healthy controls of xenobiotics (excluding drug components) originating from food consumption. Significant differences relative to healthy controls are color coded with red (increased), blue (decreased), with light ($p < 0.05$) or dark (FDR < 0.05) shades, and gray (no significant change).

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