Metformin effect on non-targeted metabolite profiles in patients with type 2 diabetes and multiple murine tissues

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Abstract:

Metformin is the first-line oral medication to increase insulin sensitivity in patients with type 2 diabetes (T2D). Our aim is to investigate metformin's pleiotropic effect using a non-targeted metabolomics approach. We analyzed 353 metabolites in fasting serum samples of the population-based human KORA F4 cohort. To compare T2D patients treated with metformin (mt-T2D, n=74) and those without antidiabetic medication (ndt-T2D, n=115), we used multivariable linear regression models in a cross-sectional study. We applied generalized estimating equation to confirm the initial findings in longitudinal samples of 683 KORA participants. In a translational approach, we used murine plasma, liver, skeletal muscle, and epididymal adipose tissue samples from metformin treated-db/db mice to further corroborate our findings from the human study. We identified two metabolites significantly (P<1.42E-04) associated with metformin treatment. Citrulline showed lower values and an unknown metabolite X-21365 showed higher relative concentrations in human serum when comparing mt-T2D with ndt-T2D. Citrulline was confirmed to be significantly (P<2.96E-04) decreased at seven years' follow up in patients who started metformin treatment. In mice, we validated significantly (P<4.52E-07) lower citrulline values in plasma, skeletal muscle, and adipose tissue of metformin treated animals, but not in their liver. The lowered values of citrulline we observed by using a non-targeted approach, most likely result from metformin's pleiotropic effect on the interlocked urea and nitric oxide cycle. The translational data derived from of multiple murine tissues corroborated and complemented the findings from the human cohort.

Introduction

Metformin became the first-line choice for treatment of type 2 diabetes (T2D) in the course of the UKPDS study (1). Additionally, metformin has been reported to have other pleiotropic

effects; e.g. it reduces insulin resistance (2), improves the uptake of glucose in muscle (3,4), reduces the risk for cancer (5) and lowers the values of low density lipoprotein cholesterol (LDL-C) (6). The underlying mechanism of the reduction of LDL-C is, at least in part, due to the activation of the AMP-activated protein kinase (AMPK) in the liver (7). Apart from that, AMPK affects several processes such as nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS) (8), which is also stimulated by metformin (9). However metformin's mode of action is not completely understood (10–12).

Our previous study was based on a targeted metabolomics approach to explore the effects of metformin on lipid profiles in the population-based KORA (Cooperative Health Research in the Region of Augsburg) cohort (6,13,14). Irving et al. recently reported decreased levels of arginine and citrulline as an effect of insulin sensitizer therapy in 12 metformin and pioglitazone treated individuals and 13 placebo-controls (15). Non-targeted metabolomic measurements have been applied to investigate hyperglycemia (16,17), and the effects of metformin treatment in non-diabetic individuals (18). However, none of the previous non-targeted metabolomics studies investigated metformin treatment in patients with T2D.

In this study we focused on serum metabolites associated with metformin treatment based on a non-targeted approach in a human population from the KORA cohort. A crosslink from human to mice was corroborated in multiple tissues (plasma, liver, skeletal muscle and epididymal adipose tissue) from a mouse study. Biologically relevant pathways for the identified metabolites are analyzed using bioinformatical approaches.

RESEARCH DESIGN AND METHODS

Ethics Statement

All participants gave written informed consent. The KORA study was approved by the ethics committee of the Bavarian Medical Association, Germany.

Approval for Mouse Study

Within this study, all mice were bred and housed in a temperature- and humidity- controlled environment in compliance with FELASA protocols. Animal experiments were approved by the District Government of Upper Bavaria (Regierung von Oberbayern, Gz.55.2-1-54-2531-70-07, 55.2-1-2532-153-11).

KORA Cohort

KORA is a population-based cohort study conducted in Southern Germany (14). The baseline survey 4 (KORA S4) consists of 4,261 individuals (aged 25-74 years) examined between 1999 and 2001. During the years of 2006 to 2008, 3,080 individuals took part in the follow-up survey 4 (KORA F4). Clinical data for each participant were retrieved from medical records. Based on fasting glucose, 2-h post-glucose load, physician-validated, and self-reported diagnoses, KORA participants were classified according to the WHO diagnostic criteria. A further grouping of patients with T2D was based on information on medication (19,20) (Table 1). Only participants with metabolite measurements were included in the present analysis (Metabolon, n=1,768 in KORA F4). We excluded i) participants with overnight non-fasting serum samples (n=8), ii) patients suffering from type 1 diabetes and drug-induced (e.g. via steroids) diabetes (n=6), iii) T2D patients treated with insulin (n=16) or both insulin and metformin (n=13), iv) patients taking glucose-lowering oral medication other than metformin (n=17). Furthermore, participants with isolated impaired fasting

glucose (IFG) (n=77) were excluded. We have previously shown that IFG and impaired glucose tolerance (IGT) should be considered as two different phenotypes (21).

In KORA F4, we focused on four groups: 1) participants with normal glucose tolerance (NGT); 2) Pre-diabetic individuals with IGT; 3) T2D patients without glucose-lowering treatment (non-anti-diabetic drug treated, ndt-T2D); and 4) Metformin treated type 2 diabetes (mt-T2D) patients (Table 1).

The same exclusion and classification criteria were used in the longitudinal analyses. We only considered participants with metabolite measurements in both studies (S4 and F4, n=818) and we excluded at both time points i) participants with overnight non-fasting serum samples (n=88), which also contained patients suffering from type 1 diabetes or drug-induced diabetes, ii) participants taking oral glucose-lowering medication other than metformin (n=11), iii) participants with insulin treatment (n=3), and iv) participants with a missing diabetes status (n=33). The remaining 683 participants were ndt-T2D, individuals with pre-diabetes and healthy controls at baseline KORA S4, 37 of them started metformin treatment at KORA F4.

The data from the KORA S4 and F4 studies, including metabolite concentrations with clinical phenotypes are available upon request through the platform KORA-PASST (Project application self-service tool) (www.helmholtz-muenchen.de/kora-gen).

Blood Sampling

In the KORA cohort study, blood was drawn into Monovette serum tubes (Sarstedt AG & Co., Nümbrecht, Germany) in the morning between 8:00 A.M. and 10:30 A.M. after at least 8 hours of fasting. Tubes were gently inverted twice, followed by 30 minutes resting at room temperature to obtain complete coagulation. For serum collection, blood was centrifuged at

2,750 g at 15 °C for ten minutes. Serum was filled into synthetic straws, which were stored in liquid nitrogen (-196 °C) until metabolomic analyses.

Non-targeted Metabolite Profiling

The serum samples from participants of the baseline KORA S4 and follow-up KORA F4 study were measured with the Metabolon analytical system (Metabolon Inc., Durham, North Carolina, USA). Metabolon applied a non-targeted semi-quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) and gas chromatography mass spectrometry (GC-MS) platform for the identification of structurally named and unknown molecules (22,23). We measured 363 (including 109 unknown) metabolites in fasting serum samples from the KORA baseline survey 4 (S4). In the seven-year follow-up survey 4 (F4) 353 metabolites (including 107 unknown) were determined (24).

In this study, we applied the same criteria for quality control as described by Albrecht et al. (25). In brief, metabolites with more than 20% missing values were excluded as were samples with more than 10% missing metabolites (25). All normalized relative ion counts were log transformed and the remaining data is imputed with Multivariate Imputation by Chained Equations (MICE) (26). We used 363 metabolites in KORA S4 and 353 metabolites in KORA F4 (Supplementary Table 1). The number of overlapping metabolites in S4 and F4 is 312. Metabolite names were used according to Shin et al. (27); however, the identity of metabolite ID M32654 and the molecule "3-dehydrocarnitine*" could not be confirmed. We therefore used the name X-21365 (Supplementary Table 1).

Each metabolite is standardized with a mean of zero and a standard deviation of one in each study after the exclusion of non-fasting participants.

Metformin Mouse Intervention Study

Pharmacological studies were conducted in 20 male 8-week old diabetic BKS.Cg-*Dock7*^{m}+/+ *Lepr*^{db}/J (db/db) mice, that were bred and housed in a temperature- and humidity-controlled environment in compliance with FELASA protocols. To exclude estrous cycle related influences on metabolic parameters, only male mice were included in this study. From an age of three weeks, all mice were fed a high-fat diet (S0372-E010, ssniff Spezialdiäten, Soest, Germany) containing [gm%] palm fat [13.5], sunflower oil [13.5], starch [30], saccharose [10], casein [20], lignocellulose [5], mineral+vitamin mix [5+2], safflower-oil [0.5], linseed-oil [0.5] to manifest a uniform diabetic phenotype. Animals received either vehicle (5% solutol/95% hydroxyethylcellulose) without (n=10) or with metformin (300 mg/kg; Sigma Aldrich, Taufkirchen, Germany, n=10) *via* gavage once daily between 5:00-6:00 P.M. before dark-phase onset (6:00 P.M.) for 14 days. Eighteen ±2 hours after the last treatment, four-hour fasting mice were sacrificed with an isoflurane overdose and organs and blood immediately collected (4). Murine plasma was prepared from whole blood by centrifugation at 4 °C, tissues were freeze-clamped; both were stored at -80 °C until further analyses. All samples were measured with the Metabolon analytical system Metabolon (Metabolon Inc., Durham, North Carolina, USA). Metabolites with more than 20% missing values were excluded as well as samples with more than 10% missing metabolites (25). All normalized relative ion counts were log transformed and the remaining data was imputed with MICE (26). Linear regression was done on metabolite values for metformin treated mice as the cases as well as for the non-metformin treated, vehicle-gavaged mice as the controls. A metabolomics examination was done for plasma, liver, skeletal muscle and epididymal adipose tissue (Table 5, Figure 1B).

Statistical Analysis

To evaluate the effect of metformin treatment on certain metabolites, multivariable linear regression models were conducted with the relative metabolite concentration values as outcome and the grouping variable as predictor. Each metabolite was assessed individually. To consider potential risk factors and confounding parameters with known effect on metabolite profiles (6,13,28–32), two models were used: 1) adjusted for age and sex as the crude model; 2) adjusted for age, sex, body mass index (BMI), physical activity, high alcohol intake, smoking status, systolic blood pressure (BP), HbA_{1c}, fasting glucose, high density lipoprotein cholesterol (HDL-C), triglycerides as well as the use of statins, beta blockers, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) as the full model. The association of conventional risk factors of T2D, as well as other population characteristics with metformin treatment was calculated via Chi-squared test for categorical variables. Shapiro–Wilk test was applied to test continuous variables for normal distribution ($P \leq 0.05$ for non-normally distributed variables, $P > 0.05$ for normally distributed variables), followed by Student's t-test for normally distributed continuous variables and Wilcoxon test for non-normally distributed continuous variables.

To account for multiple testing for the linear models, Bonferroni correction was applied and only metabolites with $P < 0.05/353 = 1.42E\text{-}04$ were considered to be statistically significantly different in KORA F4. In addition, we calculated the adjusted *P*-value with the false discovery rate (FDR), using the Benjamini-Hochberg method, which is not as stringent as the Bonferroni correction. For the full linear models, participants were excluded due to missing information of considered confounders. This led to 1,138 NGT (after exclusion of five individuals due to missing confounding information), 272 IGT, 114 ndt-T2D (after exclusion of one individual due to missing confounding information) and 70 mt-T2D (after exclusion of four individuals due to missing confounding information) participants.

In the KORA S4 to F4 longitudinal study (S4 → F4), generalized estimating equations (GEE) were used to validate the significant metabolites in both crude and full models.

All statistical analyses were performed in R (version 3.2.2) (33).

Pathway Analysis

Pathways were explored using databases, considering tissue and organ specificity. The link from observed significant metabolites to the interacting enzymes was drawn using HMDB (34). Protein-protein interactions were analyzed with STRING (35) and KEGG (36). To consider drug-related effects of metformin on certain targets, we used DrugBank (37). The link between metformin targets and the protein network was analyzed using KEGG (36).

RESULTS

Population Characteristic of Human and Mouse Studies

Based on the available non-targeted metabolomic profiles, our human discovery study, KORA F4, includes 1,143 NGT, 272 IGT, 115 ndt-T2D and 74 mt-T2D (Table 1). Among the four groups, mt-T2D patients were the oldest, more frequently men, had the highest values of HbA_{1c}, fasting glucose, triglycerides, BMI and waist circumference (Table 1).

The longitudinal KORA study includes samples of 683 participants without metformin treatment at baseline, 37 of whom were treated with metformin in the seven-year follow-up (Table 2).

From the metformin treated mice, we obtained ten samples for plasma, liver and epididymal adipose tissue and nine samples for skeletal muscle. In the same amount of

vehicle-gavaged control mice, we obtained ten samples for plasma, liver, epididymal adipose tissue and skeletal muscle.

Two Metabolites are Associated with Metformin Treatment in a Human Cross-sectional Study

Two out of the 353 used metabolites (citrulline and X-21365) were found to be significantly (P<1.42E-04) associated with metformin treatment, when comparing mt-T2D with ndt-T2D patients in the cross-sectional KORA F4 study (Table 3 and Figure 1A). Using multivariable linear regression models, we detected negative β-estimates for both the crude (β=-0.75, P=2.31E-05) and full adjustment (β=-0.79, P=2.54E-05) for citrulline. Hence, the relative concentration of citrulline is significantly lower in mt-T2D compared to ndt-T2D. By contrast, the relative concentration of X-21365 was significantly higher in mt-T2D patients than in ndt-T2D patients (Table 3 and Figure 1A). When applying the FDR, no additional associations were found to be significant in both crude and full model (Supplementary Table 3). When applying a significance cutoff of P<0.05 to the comparison of mt-T2D with ndt-T2D for the models with crude and full adjustment, 44 additional metabolites were found, including ornithine, arginine and urea (Supplementary Table 3).

Five additional pairwise comparisons between the four groups (NGT, IGT, ndt-T2D, mt-T2D) confirmed that these two metabolites are specific for metformin treatment and not due to the progression of the disease. The relative concentration of citrulline was significantly lower in mt-T2D than in the NGT and IGT groups, while the concentration of X-21365 was significantly higher (Figure 1A, Supplementary Table 2). Consistently, none of the two metabolites showed a significantly different relative concentration in the pairwise comparisons among the three groups without metformin treatment, i.e., NGT, IGT and ndt-T2D (Figure 1A, Supplementary Table 2).

The Spearman correlation coefficient between the two metabolites was low (r=0.06). We observed similar associations between the two metabolies with a number of risk factors of T2D (-0.19<r<0.19), when considering 189 individuals with ndt-T2D and mt-T2D in KORA F4 (Supplementary Figure 1).

Metformin Treatment is Associated with Decreased Blood Citrulline Values in a Human Longitudinal Cohort

The two metformin-associated metabolites were further investigated in the prospective KORA study. In 37 patients who started metformin treatment during the seven-year follow-up, citrulline was found to be significantly (Bonferroni cut-off for two identified metabolites $P<0.05/2=0.025$) decreased in longitudinal in both the crude (β=-0.67, P=2.03E-05) and the full model (β=-0.61, 2.96E-04, Table 4). In the same group, X-21365 was significantly increased in the crude (β=0.41, P=5.62E-03), but not in the full model (β=0.16, P=0. 374, Table 4).

Lower Citrulline Relative Concentrations in Plasma, Skeletal Muscle and Epididymal Adipose Tissue Confirmed in Metformin treated Mice

Consistent with the results in human, we observed significantly lower plasma citrulline relative concentrations in db/db mice following daily, subchronic metformin treatment, compared with the vehicle-gavaged control mice (β=-0.39, P=2.56E-07, Table 5, Figure 1B). In addition, we found significantly lower values of citrulline in both skeletal muscle (β=-0.35, P=1.79E-09) and epididymal adipose tissue (β=-0.26, P=4.52E-07). However, citrulline values in the liver did not differ between the metformin treated and vehicle-gavaged non-metformin treated db/db animals (β=-0.02, P=0.258, Table 5, Figure 1B). Significantly different relative concentrations of X-21365 were not found in plasma, skeletal muscle,

epididymal adipose tissue, or liver of metformin treated mice when compared to the controls (Table 5, Figure 1B).

DISCUSSION

We found significantly lower values of citrulline and significantly higher values of X-21365 in the serum of T2D patients who underwent metformin treatment compared to the non-treated patients. Additionally, using longitudinal settings, we observed that the values of citrulline significantly decreased in patients after they started metformin treatment during the follow-up. A mouse intervention study using metformin confirmed the lower values of citrulline in plasma, as well as in skeletal muscle and epididymal adipose tissue, but not in liver. Citrulline is a non-proteinogenic amino acid, the product of anabolic and the substrate of catabolic processes (38,39). It is synthesized from arginine by releasing NO, which is involved in the regulation of numerous processes in the nervous system, the immune system, as well as the cardiovascular system (8). Additionaly, citrulline is produced from ornithine in the urea cycle (38). We observed ornithine, urea and arginine, to be lowered in human serum (Figure 1C). Consistently in our previous study, which was based on a targeted metabolomicas approach, ornithine was found to be significantly lower in the metformin treated T2D-patients of the KORA F4 study. Citrulline was not measured in the targeted panel we used (6).

Metformin activates AMPK in the liver and muscle (7,40). AMPK, in turn, may stimulate eNOS by its phosphorylation (8,41), which suggests a consequent increase of the NO production in the NO cycle (Figure 1C). It is known that elevated production of NO is reflected by increased values of citrulline in urine (42), as citrulline can be used as a surrogate marker for NO (43). The decreased values of citrulline and its precursors in blood, skeletal muscle and epididymal adipose tissue, as were observed in our study, are most likely

due to an accountable, increased excretion of this metabolite. However, urine samples were not available in this study. To confirm this assumption, further studies are necessary.

Furthermore, the lower values of citrulline and arginine we observed are likely to be a consequence of the activation of eNOS. In the NO cycle, eNOS catalyzes the reaction from arginine to citrulline, thereby releasing NO (9,38). NO in turn has beneficial cardiovascular effects. The reason is that NO influences smooth muscles and activates their relaxation (44). This underlies the clinical practice guidelines, which have recommended the usage of metformin as first-line therapy in T2D patients with CVD, mainly in patients with observed reduced NO levels (45). Additional intake of citrulline to compensate the lower values of citrulline and arginine might even increase metformin's beneficial effects on CVD (46).

Additionally, citrulline is synthesized in the urea cycle, which is strongly interlocked with the NO cycle (Figure 1C). In mammals, both cycles primarily take place in the liver, but also in the kidney (47). The same accounts for the NO cycle, where arginine also plays an important role. In fact, similar effects on the urea and NO cycle were mentioned by Irving et al. (15). Their study design focussed on plasma samples of 25 male, overweight or obese participants. Furthermore all 12 metformin treated participants were additionally treated with pioglitazone (15). Our findings in multiple tissues of mice that were exclusively treated with metformin and serum of 189 T2D patients enable a deeper understanding of the underlying mode of action.

The observation that the citrulline values are not affected in the liver of metformin treated mice is presumably a consequence of the hepatic localization of the consecutive production of citrulline in both the NO and the urea cycle (38), which conserves a state of equilibrium. This is in line with observations in a recent study (18). Furthermore, significantly decreased ornithine values were found in plasma of non-diabetic individuals (18).

Apart from the NO and urea cycle, there are additional physiological processes to produce citrulline. The metabolite is also synthesized from other amino acids. Examples for such precursors are glutamine, which is converted in the enterocytes, or proline and glutamate (38). However, we did not observe any significant concentration difference for these metabolites in our human cohort.

X-21365 was not found to be significantly higher in the fully adjusted longitudinal analyses of the KORA S4 → F4 cohort although it was significant in both cross sectional analyses and in the longitudinal analyses with crude adjustment. In mice, we did not observe significant differences of X-21365 in any of the examined tissues. Recent advances in the identification of metabolites spectra suggest that this unknown metabolite (X-21365) might be 5-trimethylaminovalerate and therefore closely related to the gut microbiome which is in line with a recent study (48). Additional studies using both, blood and stool samples have to be conducted, to confirm this.

The values of metabolites in humans of the KORA study are influenced by multiple factors, such as age, sex, BMI, lifestyle, clinical measurements, and medication (6,13,28–32). We therefore considered these factors in the models underlying to our cross-sectional discovery and longitudinal investigations in a human cohort. Considering the mouse study, there was no need for a comparable adjustment, as the animals were kept under strict laboratory conditions.

Due to the physiological similarity we used data from a mouse study to not only corroborate our findings in humans, but extend our investigations on other tissues. However, our findings are limited by the comparison of metabolic analytes in two different blood matrices and species: human serum and mouse plasma. In theory, the analytical method could be affected by the difference in matrix, and delicate analytes could deteriorate during the prolonged preparation time of serum compared to plasma. Therefore, a direct comparison

between the matrices serum and plasma has limitations (49). With respect to this, we compared the serum-metabolites only in human and the plasma-metabolites only within mice and each mice tissue separately (50). The observational nature of cohort studies, and the applied methods are of purely statistical character, still they offer the opportunity to identify unknown coherences and to design study settings to confirm underlying mechanisms. Due to the fact that NO is below the mass cut-off imposed on the instruments, our investigations did not contain measurements of this chemical compound. Nevertheless, our observations suggest further investigations with a specific design to address the involvement of the NO and urea cycle in metformin treatment.

In summary, we observed that serum values of citrulline were reduced under metformin treatment in human patients with T2D and, in a translational approach, also in plasma, skeletal muscle and epididymal adipose tissue of diabetic mice. The underlying mechanism is most likely the metformin-induced activation of AMPK and its consequent increase of eNOS activity, which is linked to citrulline by the NO cycle.

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Dr. Rui Wang-Sattler, Helmholtz Zentrum München GmbH, is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

KORA

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Author's Contributions

G.K., R.W-S. conceived and designed the current study. J.Adam, J.L., T.X., J.B analyzed the data and interpreted the results. M.F.S., M.H., C.H., W.R., G.G., J.A., T.I., K.Str., R.P.M., S.N., M.RdA., C.G, A.P., K.Suh., G.K. performed the experiments, including metabolic profiling. M.F.S., S.N., R.P.M., J.L., C.H., M.Rot., M.T., S.C., Y.L., D.A., T.M., M.Rod. assisted in manuscript generation. J.Adam, S.B., R.W-S. wrote the manuscript.

Competing Financial Interests

We declare that we have no competing interests.

Duality of Interest Statement:

M.F.S. was employed at Helmholtz Zentrum München GmbH during the execution of this study. He is currently an employee of the Diabetes Medical Department of AstraZeneca GmbH (Wedel, Germany), however, the company was not involved in work related to data and manuscript generation.

S.N. was employed by the Helmholtz Zentrum München GmbH during the execution of this study. She is currently an employee of Sanofi Aventis Deutschland GmbH, however, the company was not involved in work related to data and manuscript generation.

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Table 1. Characteristics of the KORA F4 cross-sectional study samples (n=1,604)

KORA F4 study characteristics (including solely subjects with available Metabolon measurements); Percentages of individuals or means (standard deviation) are shown for each variable and each group (NGT, IGT, ndt-T2D and mt-T2D). NGT, normal glucose tolerance; IGT, impaired glucose tolerance; ndt-T2D, non-anti-diabetic drug treated type 2 diabetes; mt-T2D, metformin treated type 2 diabetes; BMI, body mass index; h, hour; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

Clinical parameters	**NGT**	**IGT**	**ndt-T2D**	**mt-T2D**
n	1,143	272	115	74
Age, years	58.9 (8.5)	63.8 (8.1)	65.1 (7.1)	66.2 (7.5)
Male, %	45	50	61	58
BMI, kg/m^2	27.0 (4.3)	29.8 (4.7)	31.0 (4.8)	32.0 (5.6)
Waist, cm	92 (12.9)	100.2 (14.3)	104.9 (12.1)	106.7 (13.0)
Physical activity, % > 1h per week	63	54	48	36
High alcohol intake*, %	20	18	25	19
Smoker, %	18	8	12	15
Systolic BP, mmHg	121.6 (17.7)	129.0 (19.0)	134.3 (19.2)	130.7 (18.2)
HDL-C, mg/dL	58.9 (14.8)	54.4 (14.2)	49.6 (11.5)	50.4 (9.6)
LDL-C, mg/dL	140.7 (34.3)	144.5 (36.2)	136.6 (36.0)	124.1 (28.3)
Total cholesterol, mg/dL	223.4 (37.7)	226.4 (41.5)	214.1 (37.0)	203.8 (37.8)
Triglycerides, mg/dL	118.5 (84.6)	150.7 (89.0)	172.5 (128.7)	177.5 (140.5)
HbA_{1c}, %	5.4 (0.3)	5.6 (0.3)	6.3 (0.9)	6.8 (1.1)
HbA_{1c}, mmol/mol	35.7 (3.2)	38.1 (3.9)	44.91 (9.9)	51.2 (11.6)
Fasting glucose, mg/dL	93.2 (7.5)	101.2 (10.6)	126.6 (30.5)	142.0 (36.0)
2-h post-glucose load, mg/dL	100.8 (20.6)	162.6 (17.5)	216.0 (50.7)†	-
Time since diagnosis, years	-	-	1.4 (2.6)‡	7.4 (6.6)
Insulin, µlU/mL	7.1 (26.1)	10.1 (10.9)	14.3 (14.3)	11.6 (11.0)
Leptin, ng/mL	17.2 (19.2)	24.2 (21.3)	26.8 (21.2)	27.8 (25.0)
Statin usage, %	12	15	28	36

Beta blocker usage, %	16	31	43	38
ACE inhibitor usage, %	10	21	32	45
ARB usage, %	8	10	17	14
Insulin therapy, %	0	0	0	0
Metformin usage, %	0	0	0	100
Parental Type 2 Diabetes, %	28	30	37	49

* ≥20g/day for women; ≥40g/day for men

† n=81;

‡ For newly diagnosed T2D patients (n=74), years since T2D diagnosis was defined as 0

NGT = Normal Glucose Tolerance; IGT = Impaired Glucose Tolerance; mt = metformin treated; ndt = non-drug treated; T2D = Type 2 Diabetes

Table 2. Characteristics of the KORA S4 → F4 prospective study samples (n=683)

Percentages of individuals or means (standard deviation) of participants (with available Metabolon measurements for S4 and F4) are shown for each variable and each group. Abbreviations: w/o, without; w/, with; ndt-T2D, non-anti-diabetic drug treated type 2 diabetes; mt-T2D, metformin treated type 2 diabetes; BMI, body mass index; h, hour; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

Clinical parameters	**Baseline S4: w/o metformin§ Follow-up F4: w/o metformin§**			**Baseline S4: w/o metformin§ Follow-up F4: w/ metformin**		
	S4	**F4**	***P*-value**	**S4**	**F4**	***P*-value**
n	646	646	-	37	37	-
Age, years	61.4 (4.2)	68.5 (4.2)	-	63.4 (3.8)	70.4 (3.9)	-
Male, %	51	51	-	54	54	-
BMI, kg/m^2	27.9 (3.9)	28.2 (4.2)	0.2	32.8 (4.3)	32 (4.5)	0.49‖
Waist, cm	93.9 (11.0)	96.8 (11.9)	1.72E-05	106.3 (11.3)	106.7 (12.3)	0.87‖
Physical activity, % > 1h per week	47	57	5.47E-04	32	43	0.47
High alcohol intake* ,%	20	19	0.65	27	16	0.4

Smoker, %	13	8	9.00E-03	14	8	0.71
Systolic BP, mmHg	132.1 (18.7)	128.2 (19.6)	3.12E-04	144.9 (18.1)	131.6 (18.3)	2.43E-03‖
HDL-C, mg/dL	59.1 (16.3)	56.7 (14.2)	0.02	53.4 (11.8)	52.4 (7.9)	0.69‖
LDL-C, mg/dL	154.5 (40.8)	142.5 (36.9)	1.86E-08	143.5 (37.6)	123.5 (23.6)	0.02
Total cholesterol, mg/dL	245.5 (42.0)	225.2 (40.7)	2.2E-16	234.1 (41.0)	202.1 (33.6)	5.20E-04
Triglyceride, mg/dL	129.9 (76.4)	132.7 (83.4)	0.56	170.6 (169)	154.5 (159.2)	0.79
HbA_{1c}, %	5.6 (0.3)	5.6 (0.5)	0.53	6.4 (0.9)	6.6 (0.7)	0.14
HbA_{1c}, mmol/mol	37.6 (3.7)	38.0 (5.7)	0.53	46.8 (10.3)	48.3 (7.8)	0.14
Fasting glucose, mg/dL	99.7 (10.9)	100.7 (17.6)	0.53	130.7 (30.1)	129.6 (28.3)	0.9
2-h post-glucose load, mg/dL	115.1 (37.1)	126.9 (40.8)	8.34E-09	205.5 (76.8)	-	-
Statin usage, %	10	22	8.05E-10	8	29	0.04
Beta blocker usage, %	17	31	5.16E-09	16	29	0.27
ACE inhibitor usage, %	8	21	2.72E-11	16	51	3.18E-03
ARB usage, %	3	12	3.67E-10	3	14	0.2
Insulin therapy, %	0	0	-	0	0	-
Metformin usage, %	0	0	-	0	100	-
Parental Type 2 Diabetes, %	25	25	-	47	47	-

*>40g/day in men; >20g/day in women

§Includes participants with NGT (Normal Glucose Tolerance), isolated IFG (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance) and ntd-T2D (non-drug treated-Type 2 Diabetes)

‖Normally distributed (every other distribution is not normal distributed)

Table 3. Two human serum metabolites significantly associated with metformin treatment in a cross sectional analyses (KORA F4)

Estimates (β) and *P*-values for the comparison of 189 participants (74 metformin treated type 2 diabetes patients (mt-T2D) and 115 non-anti-diabetic drug treated T2D patients (ndt-T2D)) were calculated using linear regression analysis with the crude and full adjustments. CI denotes confidence intervals, s.d. standard deviation. Due to missing confounding information, the models with full adjustment were based on fewer participants.

	Crude linear model			**Full linear model**		
	mt-T2D (n=74) versus ndt-T2D (n=115)			**mt-T2D (n=70)¶ versus ndt-T2D (n=114)¶**		
Metabolite	β (95% CI) per s.d.	*P*-value	FDR	β (95% CI) per s.d.	*P*-value	FDR
Citrulline	-0.75 (-1.09, -0.41)	**2.31E-05**	**2.83E-04**	-0.79 (-1.15, -0.43)	**2.54E-05**	**2.83E-04**
X-21365	0.67 (0.38, 0.96)	**7.54E-06**	**1.42E-04**	0.65 (0.34, 0.97)	**5.20E-05**	**1.42E-04**

Significant metabolites are highlighted in bold with respect to Bonferroni correction (*P*<0.05/353=1.42E-04) or the false discovery rate (FDR).

¶After exclusion of individuals due to missing confounding information

Table 4. Citrulline remaines significantly associated with metformin treatment in human serum in a longitudinal analysis (KORA S4 → F4)

Generalized estimating equation (GEE) model with crude and full adjustment was used to assess the associations between metformin treatment and metabolite serum values in the longitudinal study of 683 participants with no anti-diabetic medical treatment at baseline KORA S4. Of these participants, 37 started metformin treatment after the baseline KORA S4 study. Due to missing confounding information, the models with full adjustment were based on fewer participants.

	Crude GEE model			**Full GEE model**		
	mt-T2D (n=37) versus non-metformin treated (n=646) participants[§]			**mt-T2D (n=33)**[¶] **versus non-metformin treated (n=629)**[¶] **participants**[§]		
Metabolite	β (95% CI) per s.d.	*P*-value	FDR	β (95% CI) per s.d.	*P*-value	FDR
Citrulline	-0.67 (-0.98, -0.36)	**2.03E-05**	**1.76E-03**	-0.61 (-0.94, -0.28)	**2.96E-04**	**3.21E-04**
X-21365	0.41 (0.12, 0.69)	**5.62E-03**	0.011	0.14 (-0.17, 0.45)	0.374	0.024

Significant metabolites are highlighted in bold with repsect to Bonferroni correction ($P<0.05/2=0.025$), and the false discovery rate (FDR).

[§]Includes participants with NGT (Normal Glucose Tolerance), isolated IFG (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance) and ntd-T2D (non-drug treated - type 2 diabetes)

[¶]After exclusion of individuals due to missing confounding information

Table 5. Metabolites significantly associated with metformin treatment in mouse models

Estimates (β) and *P*-values for the comparison between metformin treated (n=10, in skeletal muscle (n=9)) and non-treated mice (n=10) sacrificed at four hours after the last treatment. CI denotes confidence intervals, s.d. standard deviation.

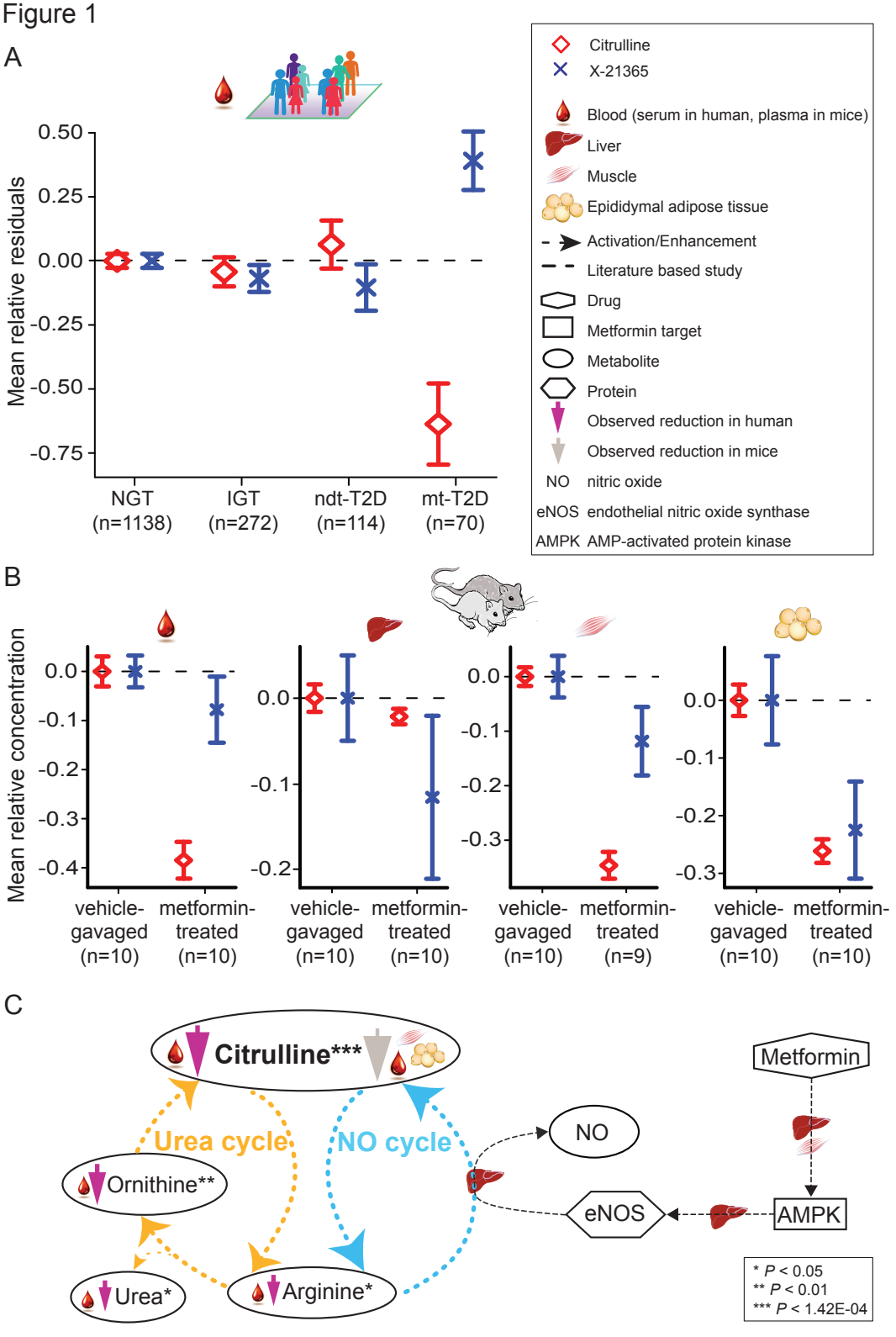
	In plasma		**In liver**		**In skeletal muscle**		**In adipose tissue**	
Metabolite	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value
Citrulline	-0.39 (-0.49, -0.28)	**2.56E-07**	-0.02 (-0.06, 0.02)	0.258	-0.35 (-0.41, -0.28)	**1.79E-09**	-0.26 (-0.33, -0.19)	**4.52E-07**
X-21365	-0.08 (-0.24, 0.08)	0.311	-0.12 (-0.34, 0.11)	0.295	-0.12 (-0.27, 0.04)	0.126	-0.23 (-0.46, 0.01)	0.063

Significant metabolites are highlighted in bold ($P<0.05$)

Figure 1 Differences in relative metabolite concentrations in a human study, in a mouse study and organ-specific pathways.

Mean relative residuals of the concentrations (with standard errors) of two metabolites for the normal glucose tolerance (NGT), impaired glucose tolerance (IGT), non-drug treated type 2 diabetes (ndt-T2D) and metformin treated type 2 diabetes (mt-T2D) groups derived in cross-sectional analysis of the KORA F4 are shown in **A**. Residuals were calculated from a linear regression model with full adjustments. Mean relative concentrations (with standard errors) of two metabolites in four different mouse tissues (plasma, liver, skeletal muscle and epididymal adipose tissue) are shown in **B**. **C**: The connections indicated by liver, muscle, and blood (plasma and serum) show organ specificity between metabolites, pathway-related proteins, metformin targets and metformin. The metabolites (ellipses) were connected to metformin treatment (straight side hexagons), proteins (hexagons), and metformin targets (rectangles). The activation/stimulation is indicated with arrows. For further information, see Tables 3, 4, 5 and Supplementary Table 2, 3.

Figure 1


A
Mean relative residuals
0.50
0.25
0.00
-0.25
-0.50
-0.75
NGT (n=1138)
IGT (n=272)
ndt-T2D (n=114)
mt-T2D (n=70)
Citrulline
X-21365
Blood (serum in human, plasma in mice)
Liver
Muscle
Epididymal adipose tissue
Activation/Enhancement
Literature based study
Drug
Metformin target
Metabolite
Protein
Observed reduction in human
Observed reduction in mice
NO nitric oxide
eNOS endothelial nitric oxide synthase
AMPK AMP-activated protein kinase
B
Mean relative concentration
vehicle-gavaged (n=10)
metformin-treated (n=10)
vehicle-gavaged (n=10)
metformin-treated (n=10)
vehicle-gavaged (n=10)
metformin-treated (n=9)
vehicle-gavaged (n=10)
metformin-treated (n=10)
C
Citrulline***
Urea cycle
NO cycle
Ornithine**
Urea*
Arginine*
NO
eNOS
AMPK
Metformin
* P < 0.05
** P < 0.01
*** P < 1.42E-04

Metformin effect on non-targeted metabolite profiles in patients with type 2 diabetes and multiple murine tissues

Supplementary material

Supplementary Table 1. Characteristics of the 525 non-targeted metabolites

The Metabolon IDs and full biochemical names of 525 metabolites (baseline KORA S4 and follow-up KORA F4) are shown in the first and second column. Metabolite names beginning with an 'X-' are denoting unknown detected metabolites. Column three and four show the status for this project (used = 'x')/excluded = '-'). Stars (*) denote unconfirmed metabolite discoveries.

Metabolite ID	Metabolite name	KORA S4	KORA F4
M00053	glutamine	x	x
M00054	tryptophan	x	x
M00059	histidine	x	x
M00060	leucine	x	x
M00063	cholesterol	x	x
M00064	phenylalanine	x	x
M00513	creatinine	x	x
M00527	lactate	x	x
M00541	4-hydroxyphenylacetate	-	-
M00542	3-hydroxybutyrate (BHBA)	x	x
M00553	cotinine	-	-
M00555	adenosine	-	-
M00569	caffeine	x	x
M00575	arabinose	-	-
M00577	fructose	x	x
M00584	mannose	x	x
M00599	pyruvate	x	x
M00606	uridine	x	x
M01105	linoleate (18:2n6)	x	x
M01107	allantoin	x	-
M01110	arachidonate (20:4n6)	x	x
M01114	deoxycholate	x	x
M01121	margarate (17:0)	x	x
M01123	inosine	-	x
M01125	isoleucine	x	x
M01284	threonine	x	x
M01299	tyrosine	x	x
M01301	lysine	x	x
M01302	methionine	x	x
M01303	malate	x	x
M01336	palmitate (16:0)	x	x
M01356	nonadecanoate (19:0)	x	x
M01358	stearate (18:0)	x	x
M01359	oleate (18:1n9)	x	x
M01361	pentadecanoate (15:0)	x	x
M01365	myristate (14:0)	x	x
M01444	pipecolate	x	x
M01481	inositol 1-phosphate (I1P)	-	-
M01493	ornithine	x	x
M01494	5-oxoproline	x	x
M01508	pantothenate	x	x
M01515	salicylate	-	-
M01558	4-acetamidobutanoate	x	x
M01561	alpha-tocopherol	x	x
M01564	citrate	x	x
M01572	glycerate	x	x
M01573	guanosine	-	x
M01585	N-acetylalanine	x	x
M01604	urate	x	x
M01605	ursodeoxycholate	x	-
M01638	arginine	x	x
M01640	ascorbate (Vitamin C)	-	x
M01642	caprate (10:0)	x	x
M01644	heptanoate (7:0)	x	x
M01645	laurate (12:0)	x	x
M01649	valine	x	x
M01670	urea	x	x
M01712	cortisol	x	x
M01769	cortisone	x	x
M01827	riboflavin (Vitamin B2)	-	-
M01898	proline	x	x

M02132	citrulline	x	x
M02137	biliverdin	-	-
M02342	serotonin (5HT)	x	x
M02730	gamma-glutamylglutamine	x	x
M02734	gamma-glutamyltyrosine	x	x
M03127	hypoxanthine	x	x
M03141	betaine	x	x
M03147	xanthine	x	x
M11438	phosphate	x	x
M12017	3-methoxytyrosine	x	x
M12032	4-acetamidophenol	-	-
M12035	pelargonate (9:0)	x	x
M12067	undecanoate (11:0)	x	x
M12122	naproxen	-	-
M12129	beta-hydroxyisovalerate	x	x
M12261	taurodeoxycholate	-	-
M12593	X-02973	x	x
M12626	X-03003	x	x
M12768	X-03088	x	x
M12770	X-03090	-	-
M12774	X-03094	x	x
M15122	glycerol	x	x
M15140	kynurenine	x	x
M15335	mannitol	x	x
M15365	glycerol 3-phosphate (G3P)	x	x
M15488	acetylphosphate	x	x
M15500	carnitine	x	x
M15506	choline	x	x
M15630	N-acetylornithine	x	x
M15650	N1-methyladenosine	x	x
M15676	3-methyl-2-oxovalerate	x	x
M15677	3-methylhistidine	-	-
M15749	3-phenylpropionate (hydrocinnamate)	x	-
M15753	hippurate	x	x
M15778	benzoate	x	x
M15958	phenylacetate	-	-
M15964	arabitol	-	x
M15990	glycerophosphorylcholine (GPC)	x	x
M15996	aspartate	x	x
M16634	X-04357	x	x
M16816	X-04494	-	-
M16818	X-04495	x	x
M16821	X-04498	x	x
M16822	X-04499 (retired for 3,4-dihydroxybutyrate)	x	X
M16823	X-04500	-	-
M17059	X-04621	-	-
M17799	ibuprofen	-	-
M17805	dihomo-linoleate (20:2n6)	x	x
M17807	X-18601	x	x
M17945	2-hydroxystearate	x	x
M18037	metoprolol	-	-
M18254	paraxanthine	x	x
M18281	2-hydroxyhippurate (salicylurate)	-	-
M18283	X-05426	x	x
M18335	quinate	x	x
M18349	indolelactate	-	x
M18357	glycylvaline	-	-
M18369	gamma-glutamylleucine	x	x
M18392	theobromine	x	x
M18394	theophylline	x	x
M18467	eicosapentaenoate (EPA; 20:5n3)	x	x
M18474	estrone 3-sulfate	-	-
M18476	glycocholate	-	-
M18477	glycodeoxycholate	-	-
M18494	taurochenodeoxycholate	x	-
M18497	taurocholate	-	-
M18929	X-05907	x	x
M19323	docosahexaenoate (DHA; 22:6n3)	x	x
M19324	1-stearoylglycerophosphoinositol	x	x
M19362	X-06226	x	x
M19363	X-06227	-	x
M19364	X-06246	x	x
M19368	X-06267	x	x
M19396	X-06307	x	x
M19414	X-06350	x	-
M19415	X-06351	x	-
M19934	myo-inositol	x	x
M20489	glucose	x	x
M20675	1,5-anhydroglucitol (1,5-AG)	x	x
M20699	erythritol	x	x
M21044	2-hydroxybutyrate (AHB)	x	x

M21047	3-methyl-2-oxobutyrate	x	x
M21049	1,6-anhydroglucose	-	-
M21127	1-palmitoylglycerol (1-monopalmitin)	x	x
M21151	saccharin	-	-
M21184	1-oleoylglycerol (1-monoolein)	x	x
M21188	1-stearoylglycerol (1-monostearin)	x	-
M21630	X-08402	x	x
M22030	2-hydroxyisobutyrate	x	x
M22032	X-08766	x	-
M22116	4-methyl-2-oxopentanoate	x	x
M22130	phenyllactate (PLA)	x	-
M22138	homocitrulline	x	-
M22175	aspartylphenylalanine	x	x
M22177	levulinate (4-oxovalerate)	x	-
M22189	palmitoylcarnitine	x	x
M22481	X-08988	x	x
M22548	X-09026	x	x
M22649	X-09108	x	x
M22842	cholate	x	-
M24074	X-09706	x	x
M25459	X-10395	x	x
M25599	X-10429	x	-
M27256	X-10500	x	x
M27273	X-10506	x	x
M27278	X-10510	x	x
M27447	1-linoleoylglycerol (1-monolinolein)	-	x
M27513	indoleacetate	x	x
M27531	hyodeoxycholate	x	-
M27672	3-indoxyl sulfate	x	x
M27710	N-acetylglycine	x	x
M27716	bilirubin (Z,Z)	x	x
M27718	creatine	x	x
M27722	erythrose	x	x
M27728	glycerol 2-phosphate	x	-
M27738	threonate	x	x
M28354	X-10675	-	-
M30805	X-10810	x	x
M31453	cysteine	x	x
M31454	cystine	-	-
M31522	pyroglutamylglycine	-	-
M31536	N-(2-furoyl)glycine	-	-
M31548	DSGEGDFXAEGGGVR*	x	x
M31555	pyridoxate	x	x
M31591	androsterone sulfate	x	x
M31787	3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	x	x
M32197	3-(4-hydroxyphenyl)lactate	x	x
M32198	acetylcarnitine	x	x
M32315	serine	x	x
M32319	trans-4-hydroxyproline	x	x
M32322	glutamate	x	x
M32328	hexanoylcarnitine	x	x
M32338	glycine	x	x
M32339	alanine	x	x
M32346	glycochenodeoxycholate	x	x
M32348	2-aminobutyrate	x	x
M32379	scyllo-inositol	x	x
M32388	dodecanedioate	x	-
M32393	gamma-glutamylvaline	x	x
M32397	3-hydroxy-2-ethylpropionate	-	-
M32398	sebacate (decanedioate)	-	-
M32401	trigonelline (N'-methylnicotinate)	-	-
M32405	indolepropionate	x	x
M32412	butyrylcarnitine	x	x
M32418	myristoleate (14:1n5)	x	x
M32425	dehydroisoandrosterone sulfate (DHEA-S)	x	x
M32445	3-methylxanthine	-	-
M32452	propionylcarnitine	x	x
M32455	linoleamide (18:2n6)	-	x
M32458	oleamide	-	x
M32489	caproate (6:0)	x	x
M32492	caprylate (8:0)	x	x
M32497	10-undecenoate (11:1n1)	x	x
M32504	docosapentaenoate (n3 DPA; 22:5n3)	x	x
M32518	X-11204	x	x
M32549	X-02269	x	x
M32553	phenol sulfate	x	x
M32557	X-06126	x	x
M32560	X-07765	-	-
M32564	X-11247	x	x
M32578	X-11261	x	x
M32586	bilirubin (E,E)*	x	X

M32587	X-02249	x	x
M32593	heme*	x	x
M32616	X-11299	x	x
M32632	X-11315	x	x
M32634	X-11317	x	x
M32635	1-linoleoylglycerophosphoethanolamine*	x	x
M32644	X-11327	x	x
M32651	X-11334	x	x
M32654	X-21365 ~~(3-dehydrocarnitine*)~~	x	x
M32672	pyroglutamine*	x	x
M32675	C-glycosyltryptophan*	x	x
M32689	X-11372	x	-
M32691	X-11374	-	x
M32698	X-11381	x	x
M32709	X-03056 (retired for N-[3-(2-Oxopyrrolidin-1-yl) propyl] acetamide)	x	x
M32729	X-11412	x	-
M32735	X-01911	x	x
M32739	X-11422 (retired for xanthine)	x	x
M32740	X-11423 (retired for O-sulfo-L-tyrosine)	x	x
M32753	X-09789	x	x
M32754	X-11437	-	-
M32755	X-11438	x	x
M32757	X-11440	x	x
M32758	X-11441	x	x
M32759	X-11442	x	x
M32761	X-11444	x	x
M32762	X-11445 (retired for 5-alpha-pregnan-3beta,20alpha-disulfate)	-	x
M32769	X-11452	x	x
M32786	X-11469	x	x
M32787	X-11470	x	x
M32795	X-11478	x	-
M32800	X-11483	-	-
M32802	X-11485	-	x
M32808	X-11491	x	-
M32814	X-11497	x	x
M32836	HWESASXX*	x	x
M32838	X-11521	x	-
M32846	X-11529	x	-
M32847	X-11530	x	x
M32854	X-11537	-	x
M32855	X-11538	x	x
M32857	X-11540	-	x
M32863	X-11546	-	-
M32867	X-11550	x	x
M32869	X-11552	-	x
M32910	X-11593 (retired for O-methylascorbate*)	x	x
M32980	adrenate (22:4n6)	x	x
M33009	homostachydrine*	x	x
M33084	ADSGEGDFXAEGGGVR*	x	x
M33085	hydroxypioglitazone*	-	-
M33131	X-11786 (retired for methylcysteine)	-	x
M33132	X-11787	x	x
M33137	X-11792	x	-
M33138	X-11793 (retired for oxidized bilirubin*)	x	x
M33139	pioglitazone*	-	-
M33140	X-11795	x	x
M33144	X-11799	-	x
M33150	X-11805	-	x
M33154	X-11809	-	x
M33163	X-11818	x	x
M33165	X-11820	x	x
M33173	2-hydroxyacetaminophen sulfate*	-	-
M33178	2-methoxyacetaminophen sulfate*	-	-
M33183	X-11838	-	-
M33188	X-11843	-	-
M33190	X-11845	-	-
M33192	X-11847	x	x
M33194	X-11849	-	x
M33195	X-11850	-	-
M33197	X-11852	-	-
M33203	X-11858	-	-
M33204	X-11859	-	x
M33221	X-11876	-	-
M33225	X-11880	-	x
M33228	1-arachidonoylglycerophosphocholine*	x	x
M33230	1-palmitoleoylglycerophosphocholine*	x	x
M33250	X-11905	-	-
M33353	X-12007	-	-
M33359	X-12013	-	-
M33363	gamma-glutamylmethionine*	-	-
M33364	gamma-glutamylthreonine*	x	-

M33380	X-12029	-	x
M33384	salicyluric glucuronide*	-	-
M33389	X-12038	x	x
M33390	X-12039	x	x
M33391	X-12040	-	-
M33408	X-12056	-	-
M33415	X-12063	x	x
M33420	gamma-tocopherol	x	-
M33422	gamma-glutamylphenylalanine	x	x
M33423	p-acetamidophenylglucuronide	-	-
M33441	isobutyrylcarnitine	x	x
M33442	pseudouridine	x	x
M33443	valerate	x	x
M33447	palmitoleate (16:1n7)	x	x
M33453	alpha-ketoglutarate	x	-
M33477	erythronate*	x	x
M33488	lathosterol	x	-
M33507	X-12092	x	x
M33508	X-12093	-	-
M33509	X-12094	x	x
M33510	X-12095 (retired for N1-methyl-3-pyridone-4-carboxamide)	x	x
M33515	X-12100 (retired for hydroxytryptophan*)	x	x
M33531	X-12116	-	-
M33587	eicosenoate (20:1n9 or 11)	x	x
M33609	X-12188	-	-
M33610	X-12189	-	-
M33616	X-12195	-	-
M33627	X-12206	-	x
M33633	X-12212	-	-
M33637	X-12216	-	-
M33638	X-12217	x	x
M33652	X-12230	-	-
M33653	X-12231	x	x
M33658	X-12236	-	-
M33666	X-12244 (retired for N-acetylcarnosine)	x	x
M33675	X-12253	x	x
M33683	X-12261	-	-
M33685	X-12263	-	-
M33751	X-12329	-	-
M33782	X-10346	-	-
M33801	ADpSGEGDFXAEGGGVR*	x	x
M33821	1-eicosatrienoylglycerophosphocholine*	x	x
M33822	1-docosahexaenoylglycerophosphocholine*	x	x
M33833	X-12405	x	x
M33835	X-12407	-	-
M33864	X-12428	-	-
M33871	1-eicosadienoylglycerophosphocholine*	x	x
M33877	X-12435	-	-
M33883	X-12441 (retired for 12-hydroxyeicosatetraenoate (12-HETE))	-	x
M33884	X-12442 (retired for 5,8-tetradecadienoate)	x	x
M33885	X-12443	-	-
M33892	X-12450	x	-
M33901	X-12456	-	-
M33910	X-12465	x	-
M33935	piperine	x	x
M33936	octanoylcarnitine	x	x
M33937	alpha-hydroxyisovalerate	x	x
M33939	N-acetylthreonine	x	-
M33941	decanoylcarnitine	x	x
M33955	1-palmitoylglycerophosphocholine	x	x
M33957	1-heptadecanoylglycerophosphocholine	x	x
M33960	1-oleoylglycerophosphocholine	x	x
M33961	1-stearoylglycerophosphocholine	x	x
M33968	5-dodecenoate (12:1n7)	x	x
M33969	stearidonate (18:4n3)	x	x
M33971	10-heptadecenoate (17:1n7)	x	x
M33972	10-nonadecenoate (19:1n9)	x	x
M33973	epiandrosterone sulfate	x	x
M34035	linolenate [alpha or gamma; (18:3n3 or 6)]	x	x
M34040	X-12510 (retired for 2-aminooctanoic acid)	x	x
M34062	X-12524	x	x
M34106	bilirubin (E,Z or Z,E)*	x	x
M34109	metoprolol acid metabolite*	-	-
M34112	X-12544	-	x
M34123	X-12556	x	x
M34214	1-arachidonoylglycerophosphoinositol*	x	x
M34221	X-12627	x	x
M34244	X-12644	x	x
M34245	X-12645	-	-
M34283	asparagine	x	x
M34289	X-12680	-	-

M34306	X-12696	x	x
M34314	X-12704	-	-
M34321	X-12711	-	-
M34322	X-12712	-	-
M34327	X-12717	-	-
M34329	X-12719	-	-
M34336	X-12726	x	-
M34338	X-12728	-	-
M34339	X-12729	-	-
M34344	X-12734	-	-
M34350	X-12740	-	-
M34359	X-12749	x	x
M34365	3-(cystein-S-yl) acetaminophen*	-	-
M34384	stachydrine	x	x
M34389	1-methylxanthine	-	-
M34390	7-methylxanthine	-	-
M34395	1-methylurate	x	-
M34400	1,7-dimethylurate	x	-
M34404	1,3,7-trimethylurate	-	-
M34407	isovalerylcarnitine	x	x
M34409	stearoylcarnitine	x	x
M34416	1-stearoylglycerophosphoethanolamine	x	x
M34419	1-linoleoylglycerophosphocholine	x	x
M34420	bradykinin, des-arg(9)	-	x
M34441	X-12771	x	-
M34453	X-12776	x	x
M34456	gamma-glutamylisoleucine*	x	-
M34469	X-12786	x	x
M34481	X-12798	x	x
M34499	X-12816	-	-
M34513	X-12830	-	-
M34516	X-12833	-	-
M34527	X-12844	x	x
M34530	X-12847	-	-
M34533	X-12850	x	-
M34534	laurylcarnitine	x	x
M34535	X-12851	-	-
M34539	X-12855	x	-
M34674	X-12990 (retired for docosapentaenoic acid (n6-DPA))	-	x
M34732	isovalerate	x	x
M34761	X-13069	x	x
M34878	X-13183 (retired for stearamide)	-	x
M34912	X-13215	x	-
M35072	X-13372	-	x
M35114	7-methylguanine	x	x
M35126	phenylacetylglutamine	x	x
M35127	pro-hydroxy-pro	x	x
M35137	N2,N2-dimethylguanosine	-	-
M35159	cysteine-glutathione disulfide	-	x
M35160	oleoylcarnitine	x	x
M35186	1-arachidonoylglycerophosphoethanolamine*	x	x
M35187	X-13429	x	-
M35189	X-13431 (retired for nonanoylcarnitine*)	x	x
M35193	X-13435	x	x
M35240	X-13477	x	x
M35253	2-palmitoylglycerophosphocholine*	x	x
M35254	2-oleoylglycerophosphocholine*	x	x
M35255	2-stearoylglycerophosphocholine*	x	x
M35257	2-linoleoylglycerophosphocholine*	x	x
M35270	X-13496	x	x
M35305	1-palmitoylglycerophosphoinositol*	x	x
M35320	catechol sulfate	x	x
M35322	hydroquinone sulfate	-	-
M35326	X-13548	-	x
M35327	X-13549	x	x
M35331	X-13553	-	-
M35397	X-13619	x	x
M35422	X-13640	-	-
M35428	tiglyl carnitine	-	-
M35431	2-methylbutyroylcarnitine	x	x
M35433	hydroxyisovaleroyl carnitine	-	x
M35439	glutaroyl carnitine	x	x
M35451	X-13658	-	-
M35464	X-13671	x	x
M35472	2-tetradecenoyl carnitine	x	x
M35508	X-13699	-	-
M35527	4-hydroxyhippurate	x	-
M35551	X-13741	x	-
M35626	1-myristoylglycerophosphocholine	x	x
M35628	1-oleoylglycerophosphoethanolamine	x	x
M35631	1-palmitoylglycerophosphoethanolamine	x	x

M35635	3-(3-hydroxyphenyl)propionate	-	-
M35669	tetradecanedioate	x	-
M35675	2-hydroxypalmitate	x	x
M35678	hexadecanedioate	x	-
M35718	dihomo-linolenate (20:3n3 or n6)	x	x
M35754	X-13859	x	x
M35854	threitol	x	x
M35977	X-14056	x	x
M35978	X-14057	-	x
M36009	X-14086	-	x
M36095	thymol sulfate	-	-
M36097	4-acetaminophen sulfate	-	-
M36098	4-vinylphenol sulfate	x	x
M36099	4-ethylphenylsulfate	x	-
M36103	p-cresol sulfate	x	x
M36115	X-14189 (retired for leucylalanine)	-	x
M36131	X-14205 (retired for alpha-glutamyltyrosine)	-	x
M36134	X-14208 (retired for phenylalanylserine)	-	x
M36230	X-14304 (retired for leucylalanine)	-	x
M36300	X-14374	x	x
M36376	X-14450 (retired for phenylalanylleucine)	-	x
M36399	X-14473	x	x
M36468	X-14541	-	-
M36515	X-14588	x	x
M36552	X-14625	x	x
M36553	X-14626	x	-
M36559	X-14632	-	-
M36585	X-14658	-	-
M36589	X-14662	-	-
M36590	X-14663	-	-
M36593	2-linoleoylglycerophosphoethanolamine*	-	-
M36673	X-14745	-	-
M36738	gamma-glutamylglutamate	-	-
M36754	octadecanedioate	x	x
M36756	leucylleucine	x	-
M36776	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	x	x
M36802	n-Butyl Oleate	-	-
M36808	dimethylarginine (SDMA + ADMA)	x	x
M36848	3-ethylphenylsulfate*	-	-
M36850	taurolithocholate 3-sulfate	x	x
M37004	X-14977 (retired for vanillin)	-	x
M37033	carbamazepine*	-	-
M37058	succinylcarnitine	x	x
M37097	tryptophan betaine	x	x
M37104	cyclo(leu-pro)	x	-
M37112	chiro-inositol	-	-
M37190	5alpha-androstan-3beta,17beta-diol disulfate	x	x
M37198	5alpha-pregnan-3beta,20alpha-diol disulfate	x	-
M37202	4-androsten-3beta,17beta-diol disulfate 1*	x	x
M37203	4-androsten-3beta,17beta-diol disulfate 2*	x	x
M37253	2-hydroxyglutarate	x	-
M37459	ergothioneine	-	-
M37506	palmitoyl sphingomyelin	x	x
M38150	phenylalanylphenylalanine	x	x
M38178	cis-4-decenoyl carnitine	x	x
M38658	atenolol	-	-
M38768	15-methylpalmitate (isobar with 2-methylpalmitate)	x	x
M39270	1-palmitoylplasmenylethanolamine*	x	-
M39379	glycoursodeoxycholate	x	-

Supplementary Table 2. Results of pairwise comparisons for citrulline and X-21365 in the cross-sectional KORA F4 study

Estimates (β) and *P*-values for the comparison between all groups (normal glucose tolerance (NGT), impaired glucose tolerance (IGT), non-drug treated type 2 diabetes (ndt-T2D) and metformin treated type 2 diabetes (mt-T2D) participants) were calculated using linear regression analysis with the crude and full adjustments. Full adjustments have lower numbers of participants due to missings within the confounders. CI denotes confidence intervals, s.d. standard deviation.

Crude Linear Model	**mt-T2D (n=74) versus NGT(n=1143)**		**mt-T2D (n=74) versus IGT (n=272)**		**mt-T2D (n=74) versus ndt-T2D (n=115)**	
Metabolite	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value
Citrulline	-0.94 (-1.17, -0.71)	**3.17E-15**	-0.83 (-1.10, -0.56)	**3.28E-09**	-0.75 (-1.09, -0.41)	**2.31E-05**
X-21365	0.84 (0.61, 1.06)	**7.88E-13**	0.83 (0.59, 1.06)	**2.81E-11**	0.67 (0.38, 0.96)	**7.54E-06**

	ndt-T2D (n=115) versus NGT (n=1143)		**ndt-T2D (n=115) versus IGT (n=272)**		**IGT (n=272) versus NGT (n=1143)**	
	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value
Citrulline	-0.21 (-0.40, -0.03)	2.52E-02	-0.09 (-0.31, 0.12)	3.92E-01	-0.14 (-0.27, -0.02)	2.89E-02
X-21365	0.18 (-0.01, 0.36)	6.03E-02	0.16 (-0.04, 0.36)	1.15E-01	0.02 (-0.11, 0.15)	7.44E-01

Full Linear Model	**mt-T2D (n=70)¶ versus NGT (n=1138)¶**		**mt-T2D (n=70)¶ versus IGT (n=272)**		**mt-T2D (n=70)¶ versus ndt-T2D (n=114)¶**	
Metabolite	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value
Citrulline	-0.96 (-1.30, -0.62)	**3.86E-08**	-0.87 (-1.26, -0.49)	**1.06E-05**	-0.79 (-1.15, -0.43)	**2.54E-05**
X-21365	0.46 (0.13, 0.79)	6.80E-03	0.59 (0.26, 0.93)	4.58E-04	0.65 (0.34, 0.97)	**5.2E-05**

	ndt-T2D (n=114)¶ versus NGT (n=1138)¶		**ndt-T2D (n=114)¶ versus IGT (n=272)**		**IGT (n=272) versus NGT (n=1138)¶**	
	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value	β (95% CI) per s.d.	*P*-value
Citrulline	-0.15 (-0.39, 0.09)	2.23E-01	-0.07 (-0.33, 0.19)	5.88E-01	-0.10 (-0.24, 0.04)	1.47E-01
X-21365	0.00 (-0.24, 0.24)	9.93E-01	0.11 (-0.13, 0.35)	3.84E-01	-0.07 (-0.20, 0.07)	3.40E-01

Significant metabolites are highlighted in **bold** (**Bonferroni corrected (*P* < 1.42E-04) and false discovery rate (P<0.05**)

¶After exclusion of individuals due to missing confounding information

Crude Model: adjusted for age and sex

Full Model: adjusted for age, sex, body mass index, physical activity, high alcohol intake, smoking status, HbA_{1c}, fasting glucose, high density lipoprotein cholesterol, triglycerides, statin usage, beta blocker usage, angiotensin-converting-enzyme inhibitor usage and angiotensin receptor blocker usage

Supplementary Table 3. Estimates and *P*-values of all metabolites for mt-T2D versus ndt-T2D patients in the discovery KORA F4 study (n=189)

Estimates (β) and *P*-values for the comparison between metformin treated type 2 diabetes (mt-T2D, n=74) and non-drug treated type 2 diabetes (ndt-T2D, n=115) were calculated using linear regression analysis with the crude and full adjustments. Full adjustments have lower numbers of participants after exclusion of individuals due to missing confounding information within the confounders (mt-T2D, n = 114; ndt-T2D, n=70). CI denotes confidence intervals, s.d. standard deviation. Orange indicates significant metabolites with *P*<0.05; red significant metabolites with Bonferroni correction (*P*<0.05/353=1.42E-04); green indicates significant metabolites according the Benjamini-Hochberg adjusted *P*-value (*P*-value < adjusted *P*-value).

		Crude Model			Full Model		
Metabolite	Biochemical_Name	β (95% CI) per s.d.	*P*-value	Adjusted *P*-value	β (95% CI) per s.d.	*P*-value	Adjusted *P*-value
M00053	glutamine	0.34 (0, 0.68)	4.94E-02	9.63E-03	0.35 (-0.03, 0.73)	7.19E-02	1.13E-02
M00054	tryptophan	-0.25 (-0.56, 0.06)	1.09E-01	1.59E-02	-0.27 (-0.62, 0.07)	1.17E-01	1.44E-02
M00059	histidine	0.18 (-0.14, 0.5)	2.68E-01	2.41E-02	0.21 (-0.14, 0.56)	2.48E-01	2.31E-02
M00060	leucine	0.25 (-0.03, 0.54)	7.75E-02	1.25E-02	0.02 (-0.28, 0.32)	8.76E-01	4.42E-02
M00063	cholesterol	-0.3 (-0.6, 0)	4.84E-02	9.35E-03	-0.4 (-0.67, -0.13)	4.55E-03	1.42E-03
M00064	phenylalanine	-0.21 (-0.52, 0.09)	1.74E-01	1.91E-02	-0.34 (-0.66, -0.02)	3.67E-02	6.94E-03
M00513	creatinine	-0.3 (-0.59, -0.01)	3.98E-02	7.65E-03	-0.22 (-0.54, 0.09)	1.66E-01	1.87E-02
M00527	lactate	-0.08 (-0.38, 0.22)	6.03E-01	3.73E-02	-0.21 (-0.53, 0.11)	1.94E-01	2.03E-02
M00542	3-hydroxybutyrate (BHBA)	0.31 (0.03, 0.59)	3.21E-02	7.22E-03	0.31 (0, 0.61)	5.02E-02	8.64E-03
M00569	caffeine	-0.28 (-0.61, 0.04)	9.04E-02	1.35E-02	-0.29 (-0.63, 0.05)	9.40E-02	1.27E-02
M00577	fructose	-0.13 (-0.42, 0.16)	3.64E-01	2.85E-02	-0.18 (-0.48, 0.12)	2.43E-01	2.28E-02
M00584	mannose	0.27 (-0.05, 0.59)	9.67E-02	1.40E-02	-0.01 (-0.31, 0.28)	9.28E-01	4.62E-02
M00599	pyruvate	0.15 (-0.12, 0.43)	2.71E-01	2.46E-02	0.02 (-0.28, 0.32)	8.98E-01	4.50E-02
M00606	uridine	-0.09 (-0.41, 0.22)	5.59E-01	3.56E-02	-0.23 (-0.53, 0.07)	1.40E-01	1.61E-02
M01105	linoleate (18:2n6)	0.15 (-0.13, 0.43)	2.95E-01	2.59E-02	0.17 (-0.11, 0.44)	2.38E-01	2.25E-02
M01110	arachidonate (20:4n6)	-0.01 (-0.29, 0.27)	9.48E-01	4.80E-02	0.04 (-0.27, 0.35)	7.84E-01	4.16E-02
M01114	deoxycholate	0 (-0.29, 0.29)	9.88E-01	4.96E-02	-0.01 (-0.32, 0.3)	9.33E-01	4.67E-02
M01121	margarate (17:0)	0.23 (-0.05, 0.51)	1.03E-01	1.49E-02	0.14 (-0.15, 0.43)	3.44E-01	2.71E-02
M01123	inosine	0.42 (0.15, 0.7)	3.11E-03	1.98E-03	0.39 (0.08, 0.7)	1.37E-02	3.68E-03
M01125	isoleucine	0.41 (0.16, 0.65)	1.23E-03	1.13E-03	0.23 (-0.03, 0.49)	8.07E-02	1.19E-02
M01284	threonine	0.25 (-0.05, 0.54)	1.03E-01	1.47E-02	0.2 (-0.14, 0.54)	2.41E-01	2.27E-02
M01299	tyrosine	-0.17 (-0.47, 0.14)	2.76E-01	2.51E-02	-0.23 (-0.54, 0.09)	1.53E-01	1.74E-02
M01301	lysine	0.03 (-0.28, 0.35)	8.31E-01	4.48E-02	-0.09 (-0.43, 0.25)	6.08E-01	3.63E-02
M01302	methionine	0.1 (-0.18, 0.39)	4.80E-01	3.24E-02	0.08 (-0.24, 0.4)	6.18E-01	3.70E-02
M01303	malate	0.48 (0.17, 0.78)	2.63E-03	1.84E-03	0.52 (0.18, 0.86)	3.13E-03	1.13E-03
M01336	palmitate (16:0)	0.24 (-0.03, 0.51)	8.08E-02	1.30E-02	0.2 (-0.08, 0.47)	1.54E-01	1.76E-02
M01356	nonadecanoate (19:0)	0.04 (-0.23, 0.32)	7.58E-01	4.19E-02	-0.02 (-0.31, 0.27)	8.79E-01	4.43E-02
M01358	stearate (18:0)	0.25 (-0.01, 0.51)	6.23E-02	1.06E-02	0.18 (-0.09, 0.44)	1.87E-01	1.98E-02
M01359	oleate (18:1n9)	0.12 (-0.14, 0.39)	3.64E-01	2.83E-02	0.11 (-0.17, 0.38)	4.50E-01	3.14E-02
M01361	pentadecanoate (15:0)	-0.11 (-0.37, 0.16)	4.22E-01	3.06E-02	-0.22 (-0.52, 0.07)	1.31E-01	1.57E-02
M01365	myristate (14:0)	0.1 (-0.17, 0.36)	4.79E-01	3.23E-02	-0.01 (-0.29, 0.27)	9.61E-01	4.83E-02
M01444	pipecolate	0.14 (-0.17, 0.44)	3.75E-01	2.93E-02	0.15 (-0.17, 0.46)	3.63E-01	2.78E-02
M01493	ornithine	-0.51 (-0.8, -0.22)	7.78E-04	7.08E-04	-0.43 (-0.76, -0.11)	9.78E-03	2.27E-03
M01494	5-oxoproline	0.04 (-0.26, 0.34)	7.76E-01	4.24E-02	0.02 (-0.31, 0.36)	8.99E-01	4.52E-02
M01508	pantothenate	0.27 (-0.02, 0.56)	6.62E-02	1.09E-02	0.21 (-0.1, 0.51)	1.84E-01	1.94E-02
M01558	4-acetamidobutanoate	0.05 (-0.26, 0.36)	7.42E-01	4.16E-02	-0.01 (-0.35, 0.33)	9.46E-01	4.77E-02

M01561	alpha-tocopherol	-0.11 (-0.44, 0.23)	5.21E-01	3.44E-02	-0.14 (-0.46, 0.18)	3.91E-01	2.89E-02
M01564	citrate	-0.07 (-0.34, 0.2)	5.94E-01	3.67E-02	0.01 (-0.28, 0.3)	9.45E-01	4.76E-02
M01572	glycerate	-0.32 (-0.6, -0.04)	2.67E-02	6.52E-03	-0.27 (-0.58, 0.04)	9.23E-02	1.25E-02
M01573	guanosine	0.28 (0, 0.56)	5.34E-02	1.01E-02	0.28 (-0.04, 0.6)	8.60E-02	1.23E-02
M01585	N-acetylalanine	-0.15 (-0.43, 0.12)	2.80E-01	2.52E-02	-0.16 (-0.46, 0.14)	3.00E-01	2.56E-02
M01604	urate	-0.1 (-0.35, 0.16)	4.51E-01	3.17E-02	0.08 (-0.17, 0.34)	5.20E-01	3.34E-02
M01638	arginine	-0.38 (-0.7, -0.07)	1.74E-02	5.10E-03	-0.37 (-0.71, -0.03)	3.11E-02	5.67E-03
M01640	ascorbate (Vitamin C)	0.44 (0.15, 0.73)	3.57E-03	2.12E-03	0.32 (-0.01, 0.64)	5.72E-02	9.63E-03
M01642	caprate (10:0)	-0.09 (-0.4, 0.22)	5.63E-01	3.58E-02	-0.02 (-0.34, 0.3)	9.06E-01	4.58E-02
M01644	heptanoate (7:0)	-0.1 (-0.41, 0.2)	5.12E-01	3.40E-02	0.09 (-0.22, 0.39)	5.75E-01	3.54E-02
M01645	laurate (12:0)	0.09 (-0.18, 0.37)	5.05E-01	3.34E-02	0.04 (-0.26, 0.34)	7.78E-01	4.15E-02
M01649	valine	0.17 (-0.11, 0.46)	2.24E-01	2.20E-02	0 (-0.31, 0.3)	9.79E-01	4.92E-02
M01670	urea	-0.35 (-0.64, -0.06)	1.95E-02	5.52E-03	-0.31 (-0.62, 0)	4.86E-02	8.36E-03
M01712	cortisol	-0.2 (-0.52, 0.12)	2.19E-01	2.15E-02	-0.11 (-0.43, 0.22)	5.08E-01	3.29E-02
M01769	cortisone	-0.18 (-0.48, 0.11)	2.22E-01	2.17E-02	-0.08 (-0.41, 0.25)	6.45E-01	3.81E-02
M01898	proline	0.25 (-0.03, 0.53)	7.80E-02	1.26E-02	0.22 (-0.09, 0.52)	1.62E-01	1.80E-02
M02132	citrulline	-0.75 (-1.08, -0.41)	2.31E-05	2.83E-04	-0.79 (-1.15, -0.43)	2.54E-05	1.42E-04
M02342	serotonin (5HT)	0.04 (-0.26, 0.34)	7.83E-01	4.28E-02	-0.06 (-0.39, 0.26)	7.02E-01	3.98E-02
M02730	gamma-glutamylglutamine	-0.14 (-0.47, 0.2)	4.28E-01	3.10E-02	0.01 (-0.37, 0.38)	9.79E-01	4.93E-02
M02734	gamma-glutamyltyrosine	-0.42 (-0.71, -0.13)	4.22E-03	2.69E-03	-0.4 (-0.7, -0.1)	8.50E-03	2.12E-03
M03127	hypoxanthine	0.05 (-0.26, 0.36)	7.65E-01	4.21E-02	-0.17 (-0.51, 0.17)	3.21E-01	2.65E-02
M03141	betaine	-0.41 (-0.74, -0.07)	1.88E-02	5.38E-03	-0.42 (-0.78, -0.05)	2.51E-02	4.82E-03
M03147	xanthine	-0.19 (-0.55, 0.17)	3.00E-01	2.61E-02	-0.29 (-0.68, 0.09)	1.36E-01	1.60E-02
M11438	phosphate	-0.29 (-0.58, -0.01)	4.18E-02	8.07E-03	-0.41 (-0.71, -0.12)	5.69E-03	1.56E-03
M12017	3-methoxytyrosine	-0.21 (-0.49, 0.07)	1.41E-01	1.76E-02	-0.25 (-0.56, 0.06)	1.14E-01	1.43E-02
M12035	pelargonate (9:0)	-0.1 (-0.44, 0.24)	5.76E-01	3.63E-02	0.15 (-0.18, 0.48)	3.65E-01	2.80E-02
M12067	undecanoate (11:0)	0.02 (-0.29, 0.34)	8.80E-01	4.70E-02	0.16 (-0.18, 0.51)	3.52E-01	2.73E-02
M12129	beta-hydroxyisovalerate	0.03 (-0.26, 0.32)	8.44E-01	4.53E-02	-0.07 (-0.39, 0.25)	6.77E-01	3.91E-02
M12593	X-02973	-0.18 (-0.5, 0.14)	2.56E-01	2.35E-02	-0.16 (-0.52, 0.2)	3.79E-01	2.82E-02
M12626	X-03003	-0.31 (-0.6, -0.02)	3.76E-02	7.37E-03	-0.25 (-0.56, 0.06)	1.09E-01	1.39E-02
M12768	X-03088	-0.27 (-0.57, 0.03)	7.61E-02	1.23E-02	-0.33 (-0.66, 0.01)	5.44E-02	9.35E-03
M12774	X-03094	-0.1 (-0.4, 0.21)	5.26E-01	3.47E-02	-0.11 (-0.41, 0.18)	4.51E-01	3.19E-02
M15122	glycerol	-0.09 (-0.38, 0.2)	5.49E-01	3.53E-02	-0.21 (-0.49, 0.07)	1.44E-01	1.67E-02
M15140	kynurenine	-0.42 (-0.71, -0.14)	3.72E-03	2.27E-03	-0.37 (-0.66, -0.07)	1.44E-02	3.97E-03
M15335	mannitol	0.44 (0.14, 0.74)	3.97E-03	2.41E-03	0.34 (0.02, 0.66)	3.85E-02	7.51E-03
M15365	glycerol 3-phosphate (G3P)	-0.24 (-0.5, 0.02)	7.51E-02	1.22E-02	-0.25 (-0.53, 0.03)	7.97E-02	1.16E-02
M15488	acetylphosphate	-0.1 (-0.38, 0.18)	4.84E-01	3.29E-02	-0.25 (-0.55, 0.06)	1.10E-01	1.40E-02
M15500	carnitine	0.03 (-0.27, 0.34)	8.23E-01	4.42E-02	0.01 (-0.31, 0.33)	9.62E-01	4.84E-02
M15506	choline	-0.33 (-0.65, -0.01)	4.28E-02	8.50E-03	-0.37 (-0.71, -0.03)	3.53E-02	6.37E-03
M15630	N-acetylornithine	-0.04 (-0.3, 0.22)	7.78E-01	4.25E-02	0 (-0.29, 0.29)	9.97E-01	5.00E-02
M15650	N1-methyladenosine	-0.04 (-0.33, 0.24)	7.79E-01	4.26E-02	-0.09 (-0.4, 0.22)	5.75E-01	3.53E-02
M15676	3-methyl-2-oxovalerate	0.26 (0, 0.52)	4.58E-02	8.78E-03	0.2 (-0.07, 0.47)	1.53E-01	1.73E-02
M15753	hippurate	0.23 (-0.05, 0.52)	1.04E-01	1.52E-02	0.31 (0, 0.63)	4.90E-02	8.50E-03
M15778	benzoate	-0.32 (-0.67, 0.03)	6.88E-02	1.12E-02	-0.14 (-0.5, 0.22)	4.43E-01	3.10E-02
M15964	arabitol	-0.28 (-0.61, 0.05)	9.83E-02	1.43E-02	-0.3 (-0.66, 0.06)	1.02E-01	1.32E-02
M15990	glycerophosphorylcholine (GPC)	0.23 (-0.06, 0.51)	1.17E-01	1.61E-02	0.13 (-0.17, 0.43)	3.82E-01	2.83E-02
M15996	aspartate	-0.48 (-0.73, -0.23)	1.69E-04	4.25E-04	-0.35 (-0.62, -0.07)	1.31E-02	3.26E-03
M16634	X-04357	-0.22 (-0.51, 0.06)	1.28E-01	1.69E-02	-0.31 (-0.62, 0)	5.07E-02	8.78E-03
M16818	X-04495	-0.43 (-0.7, -0.16)	2.20E-03	1.56E-03	-0.38 (-0.67, -0.09)	1.06E-02	2.69E-03
M16821	X-04498	0.06 (-0.23, 0.35)	6.88E-01	3.95E-02	0.01 (-0.3, 0.33)	9.25E-01	4.60E-02
M16822	X-04499--3,4-dihydroxybutyrate	0.06 (-0.23, 0.35)	6.79E-01	3.92E-02	0.13 (-0.19, 0.44)	4.22E-01	3.02E-02
M17805	dihomo-linoleate (20:2n6)	0.15 (-0.13, 0.44)	2.87E-01	2.55E-02	0.14 (-0.14, 0.43)	3.28E-01	2.68E-02

M17807	X-18601	-0.13 (-0.43, 0.18)	4.22E-01	3.05E-02	-0.17 (-0.51, 0.16)	3.12E-01	2.61E-02
M17945	2-hydroxystearate	0.24 (-0.06, 0.55)	1.17E-01	1.60E-02	0.28 (-0.06, 0.63)	1.04E-01	1.33E-02
M18254	paraxanthine	-0.1 (-0.43, 0.23)	5.35E-01	3.50E-02	-0.1 (-0.46, 0.25)	5.71E-01	3.47E-02
M18283	X-05426	0.15 (-0.17, 0.47)	3.65E-01	2.88E-02	0.13 (-0.2, 0.47)	4.31E-01	3.03E-02
M18335	quinate	0.25 (-0.03, 0.54)	8.47E-02	1.33E-02	0.26 (-0.05, 0.57)	9.69E-02	1.29E-02
M18349	indolelactate	0.26 (-0.02, 0.53)	6.88E-02	1.13E-02	0.28 (-0.02, 0.58)	6.28E-02	1.02E-02
M18369	gamma-glutamylleucine	0.15 (-0.1, 0.41)	2.35E-01	2.24E-02	0.05 (-0.22, 0.33)	7.09E-01	4.01E-02
M18392	theobromine	-0.01 (-0.36, 0.34)	9.53E-01	4.83E-02	0.01 (-0.39, 0.41)	9.61E-01	4.82E-02
M18394	theophylline	-0.23 (-0.56, 0.1)	1.67E-01	1.87E-02	-0.22 (-0.57, 0.12)	2.07E-01	2.08E-02
M18467	eicosapentaenoate (EPA; 20:5n3)	-0.09 (-0.37, 0.19)	5.16E-01	3.43E-02	-0.08 (-0.37, 0.22)	6.18E-01	3.68E-02
M18929	X-05907	-0.03 (-0.34, 0.28)	8.49E-01	4.55E-02	-0.06 (-0.37, 0.25)	6.89E-01	3.94E-02
M19323	docosahexaenoate (DHA; 22:6n3)	-0.15 (-0.45, 0.16)	3.38E-01	2.73E-02	-0.13 (-0.46, 0.19)	4.09E-01	2.97E-02
M19324	1-stearoylglycerophosphoinositol	-0.14 (-0.45, 0.17)	3.65E-01	2.86E-02	-0.13 (-0.47, 0.21)	4.45E-01	3.12E-02
M19362	X-06226	-0.03 (-0.34, 0.29)	8.57E-01	4.60E-02	-0.18 (-0.51, 0.15)	2.87E-01	2.49E-02
M19363	X-06227	0.03 (-0.25, 0.31)	8.31E-01	4.46E-02	-0.09 (-0.38, 0.19)	5.19E-01	3.33E-02
M19364	X-06246	0.23 (-0.05, 0.51)	1.01E-01	1.44E-02	0.06 (-0.23, 0.35)	6.87E-01	3.92E-02
M19368	X-06267	-0.48 (-0.74, -0.22)	3.66E-04	5.67E-04	-0.49 (-0.77, -0.21)	7.94E-04	4.25E-04
M19396	X-06307	-0.33 (-0.67, 0)	4.77E-02	9.07E-03	-0.39 (-0.76, -0.02)	3.67E-02	7.08E-03
M19934	myo-inositol	-0.32 (-0.63, -0.01)	4.22E-02	8.36E-03	-0.32 (-0.66, 0.02)	6.20E-02	1.01E-02
M20489	glucose	0.47 (0.14, 0.81)	5.38E-03	2.97E-03	0.14 (-0.11, 0.38)	2.77E-01	2.39E-02
M20675	1,5-anhydroglucitol (1,5-AG)	-0.28 (-0.63, 0.06)	1.04E-01	1.50E-02	0.02 (-0.32, 0.35)	9.10E-01	4.59E-02
M20699	erythritol	0.29 (0.01, 0.56)	4.04E-02	7.79E-03	0.26 (-0.03, 0.55)	8.10E-02	1.20E-02
M21044	2-hydroxybutyrate (AHB)	-0.05 (-0.35, 0.24)	7.21E-01	4.05E-02	-0.13 (-0.44, 0.18)	3.97E-01	2.92E-02
M21047	3-methyl-2-oxobutyrate	0.04 (-0.22, 0.31)	7.41E-01	4.14E-02	-0.06 (-0.34, 0.22)	6.59E-01	3.84E-02
M21127	1-palmitoylglycerol (1-monopalmitin)	-0.07 (-0.37, 0.22)	6.29E-01	3.78E-02	-0.15 (-0.42, 0.13)	2.94E-01	2.54E-02
M21184	1-oleoylglycerol (1-monoolein)	0 (-0.31, 0.31)	1.00E+00	5.00E-02	-0.03 (-0.32, 0.25)	8.16E-01	4.25E-02
M21630	X-08402	-0.18 (-0.46, 0.1)	1.98E-01	2.07E-02	-0.35 (-0.63, -0.06)	1.77E-02	4.25E-03
M22030	2-hydroxyisobutyrate	0.17 (-0.15, 0.48)	2.89E-01	2.56E-02	0.17 (-0.17, 0.51)	3.24E-01	2.66E-02
M22116	4-methyl-2-oxopentanoate	0.12 (-0.16, 0.39)	4.04E-01	2.99E-02	0.07 (-0.24, 0.37)	6.67E-01	3.87E-02
M22175	aspartylphenylalanine	-0.57 (-0.91, -0.24)	8.30E-04	8.50E-04	-0.62 (-0.98, -0.26)	8.67E-04	5.67E-04
M22189	palmitoylcarnitine	0.13 (-0.14, 0.4)	3.32E-01	2.72E-02	0.17 (-0.1, 0.44)	2.13E-01	2.14E-02
M22481	X-08988	-0.04 (-0.35, 0.27)	8.03E-01	4.35E-02	0.04 (-0.3, 0.39)	7.98E-01	4.22E-02
M22548	X-09026	0.08 (-0.2, 0.36)	5.63E-01	3.57E-02	-0.04 (-0.33, 0.26)	7.96E-01	4.21E-02
M22649	X-09108	0.26 (-0.05, 0.56)	9.70E-02	1.42E-02	0.27 (-0.06, 0.6)	1.08E-01	1.37E-02
M24074	X-09706	-0.07 (-0.36, 0.23)	6.58E-01	3.88E-02	-0.06 (-0.38, 0.27)	7.33E-01	4.05E-02
M25459	X-10395	-0.05 (-0.34, 0.23)	7.15E-01	3.99E-02	-0.06 (-0.35, 0.23)	6.95E-01	3.95E-02
M27256	X-10500	-0.24 (-0.52, 0.04)	9.13E-02	1.36E-02	-0.38 (-0.66, -0.09)	1.03E-02	2.55E-03
M27273	X-10506	0.36 (0.05, 0.66)	2.24E-02	5.95E-03	0.17 (-0.14, 0.49)	2.76E-01	2.38E-02
M27278	X-10510	-0.15 (-0.43, 0.12)	2.70E-01	2.45E-02	-0.21 (-0.49, 0.08)	1.63E-01	1.83E-02
M27447	1-linoleoylglycerol (1-monolinolein)	-0.11 (-0.42, 0.21)	5.11E-01	3.37E-02	-0.12 (-0.42, 0.18)	4.38E-01	3.09E-02
M27513	indoleacetate	-0.31 (-0.62, -0.01)	4.20E-02	8.22E-03	-0.34 (-0.69, 0)	4.78E-02	8.22E-03
M27672	3-indoxyl sulfate	0.34 (0.07, 0.6)	1.49E-02	4.67E-03	0.31 (0, 0.61)	4.71E-02	8.07E-03
M27710	N-acetylglycine	-0.08 (-0.35, 0.18)	5.25E-01	3.46E-02	0.01 (-0.28, 0.29)	9.62E-01	4.86E-02
M27716	bilirubin (Z,Z)	-0.34 (-0.61, -0.07)	1.44E-02	4.39E-03	-0.21 (-0.51, 0.08)	1.55E-01	1.77E-02
M27718	creatine	0.41 (0.12, 0.71)	6.57E-03	3.12E-03	0.35 (0.02, 0.67)	3.63E-02	6.52E-03
M27722	erythrose	-0.34 (-0.64, -0.04)	2.49E-02	6.23E-03	-0.45 (-0.77, -0.13)	6.65E-03	1.70E-03
M27738	threonate	-0.24 (-0.56, 0.07)	1.32E-01	1.71E-02	-0.12 (-0.47, 0.22)	4.86E-01	3.23E-02
M30805	X-10810	-0.3 (-0.6, 0)	4.84E-02	9.21E-03	-0.33 (-0.66, 0)	5.32E-02	9.21E-03
M31453	cysteine	-0.31 (-0.58, -0.04)	2.54E-02	6.37E-03	-0.21 (-0.5, 0.09)	1.66E-01	1.86E-02
M31548	DSGEGDFXAEGGGVR*	0.2 (-0.13, 0.52)	2.39E-01	2.25E-02	0 (-0.35, 0.35)	9.96E-01	4.99E-02
M31555	pyridoxate	0.01 (-0.24, 0.27)	9.09E-01	4.77E-02	0.07 (-0.2, 0.33)	6.21E-01	3.73E-02
M31591	androsterone sulfate	-0.37 (-0.67, -0.07)	1.67E-02	4.96E-03	-0.42 (-0.75, -0.1)	1.16E-02	2.83E-03

M31787	3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	-0.23 (-0.53, 0.07)	1.35E-01	1.73E-02	-0.3 (-0.63, 0.02)	6.90E-02	1.10E-02
M32197	3-(4-hydroxyphenyl)lactate	-0.33 (-0.59, -0.08)	1.14E-02	3.97E-03	-0.28 (-0.55, -0.02)	3.34E-02	5.81E-03
M32198	acetylcarnitine	-0.09 (-0.35, 0.17)	4.94E-01	3.31E-02	0.01 (-0.26, 0.29)	9.29E-01	4.65E-02
M32315	serine	0.07 (-0.22, 0.37)	6.25E-01	3.77E-02	-0.01 (-0.35, 0.32)	9.35E-01	4.72E-02
M32319	trans-4-hydroxyproline	-0.36 (-0.66, -0.06)	1.79E-02	5.24E-03	-0.39 (-0.73, -0.06)	2.23E-02	4.67E-03
M32322	glutamate	-0.12 (-0.39, 0.14)	3.54E-01	2.79E-02	-0.25 (-0.53, 0.03)	8.06E-02	1.18E-02
M32328	hexanoylcarnitine	-0.1 (-0.37, 0.17)	4.57E-01	3.20E-02	-0.12 (-0.41, 0.17)	4.22E-01	3.00E-02
M32338	glycine	0.1 (-0.14, 0.34)	4.12E-01	3.00E-02	0.21 (-0.05, 0.46)	1.12E-01	1.42E-02
M32339	alanine	0.16 (-0.1, 0.42)	2.16E-01	2.12E-02	0.08 (-0.21, 0.36)	5.97E-01	3.58E-02
M32346	glycochenodeoxycholate	0.12 (-0.18, 0.42)	4.32E-01	3.13E-02	0.27 (-0.05, 0.59)	9.94E-02	1.30E-02
M32348	2-aminobutyrate	-0.1 (-0.4, 0.2)	5.13E-01	3.41E-02	-0.11 (-0.43, 0.21)	4.97E-01	3.26E-02
M32379	scyllo-inositol	-0.04 (-0.33, 0.26)	8.17E-01	4.39E-02	-0.11 (-0.43, 0.22)	5.18E-01	3.31E-02
M32393	gamma-glutamylvaline	0.02 (-0.22, 0.27)	8.64E-01	4.65E-02	-0.02 (-0.28, 0.24)	8.82E-01	4.45E-02
M32405	indolepropionate	-0.03 (-0.31, 0.26)	8.53E-01	4.58E-02	0 (-0.32, 0.32)	9.90E-01	4.96E-02
M32412	butyrylcarnitine	-0.21 (-0.48, 0.07)	1.41E-01	1.74E-02	-0.16 (-0.45, 0.13)	2.84E-01	2.48E-02
M32418	myristoleate (14:1n5)	-0.16 (-0.44, 0.12)	2.51E-01	2.32E-02	-0.22 (-0.5, 0.06)	1.22E-01	1.52E-02
M32425	dehydroisoandrosterone sulfate (DHEA-S)	-0.19 (-0.49, 0.1)	2.00E-01	2.10E-02	-0.2 (-0.52, 0.12)	2.26E-01	2.18E-02
M32452	propionylcarnitine	0.03 (-0.26, 0.31)	8.58E-01	4.62E-02	0.05 (-0.27, 0.37)	7.57E-01	4.12E-02
M32455	linoleamide (18:2n6)	0.05 (-0.22, 0.33)	6.99E-01	3.98E-02	0.15 (-0.16, 0.46)	3.38E-01	2.69E-02
M32458	oleamide	0.14 (-0.15, 0.42)	3.55E-01	2.80E-02	0.19 (-0.14, 0.51)	2.61E-01	2.32E-02
M32489	caproate (6:0)	-0.15 (-0.45, 0.14)	3.10E-01	2.65E-02	0.07 (-0.23, 0.37)	6.29E-01	3.75E-02
M32492	caprylate (8:0)	-0.06 (-0.36, 0.25)	7.20E-01	4.04E-02	0.1 (-0.21, 0.41)	5.25E-01	3.36E-02
M32497	10-undecenoate (11:1n1)	-0.41 (-0.72, -0.11)	8.66E-03	3.40E-03	-0.51 (-0.84, -0.18)	2.51E-03	9.92E-04
M32504	docosapentaenoate (n3 DPA; 22:5n3)	0.21 (-0.09, 0.52)	1.72E-01	1.90E-02	0.16 (-0.15, 0.46)	3.20E-01	2.63E-02
M32518	X-11204	-0.05 (-0.37, 0.28)	7.84E-01	4.29E-02	-0.01 (-0.33, 0.3)	9.34E-01	4.69E-02
M32549	X-02269	-0.26 (-0.56, 0.05)	9.62E-02	1.39E-02	-0.26 (-0.6, 0.07)	1.22E-01	1.50E-02
M32553	phenol sulfate	0.07 (-0.28, 0.42)	6.79E-01	3.94E-02	0.18 (-0.21, 0.57)	3.65E-01	2.79E-02
M32557	X-06126	-0.14 (-0.44, 0.17)	3.83E-01	2.95E-02	-0.03 (-0.36, 0.3)	8.69E-01	4.39E-02
M32564	X-11247	-0.04 (-0.3, 0.22)	7.50E-01	4.18E-02	0.02 (-0.27, 0.3)	9.02E-01	4.53E-02
M32578	X-11261	0 (-0.27, 0.28)	9.86E-01	4.94E-02	-0.02 (-0.32, 0.28)	8.96E-01	4.49E-02
M32586	bilirubin (E,E)*	0.13 (-0.14, 0.41)	3.44E-01	2.75E-02	0.22 (-0.07, 0.52)	1.30E-01	1.56E-02
M32587	X-02249	-0.37 (-0.68, -0.06)	2.04E-02	5.67E-03	-0.44 (-0.77, -0.12)	7.57E-03	1.98E-03
M32593	heme*	-0.03 (-0.33, 0.27)	8.61E-01	4.63E-02	0.01 (-0.32, 0.34)	9.62E-01	4.87E-02
M32616	X-11299	0.12 (-0.17, 0.41)	4.15E-01	3.02E-02	0.17 (-0.15, 0.49)	3.06E-01	2.59E-02
M32632	X-11315	-0.16 (-0.48, 0.15)	3.12E-01	2.66E-02	0.08 (-0.23, 0.39)	6.18E-01	3.71E-02
M32634	X-11317	0.04 (-0.3, 0.37)	8.24E-01	4.43E-02	0.12 (-0.19, 0.43)	4.51E-01	3.17E-02
M32635	1-linoleoylglycerophosphoethanolamine*	0.24 (-0.08, 0.56)	1.42E-01	1.77E-02	0.15 (-0.19, 0.49)	3.88E-01	2.86E-02
M32644	X-11327	0 (-0.31, 0.31)	9.89E-01	4.97E-02	0.01 (-0.3, 0.31)	9.70E-01	4.90E-02
M32651	X-11334	0 (-0.3, 0.3)	9.90E-01	4.99E-02	0.11 (-0.23, 0.44)	5.31E-01	3.41E-02
M32654	X-21365 ~~(3-dehydrocarnitine*)~~	0.67 (0.38, 0.96)	7.54E-06	1.42E-04	0.65 (0.34, 0.97)	5.20E-05	2.83E-04
M32672	pyroglutamine*	-0.27 (-0.57, 0.03)	7.46E-02	1.20E-02	-0.07 (-0.37, 0.24)	6.70E-01	3.90E-02
M32675	C-glycosyltryptophan*	-0.05 (-0.33, 0.23)	7.31E-01	4.07E-02	-0.1 (-0.4, 0.2)	5.05E-01	3.27E-02
M32691	X-11374	0 (-0.3, 0.31)	9.83E-01	4.92E-02	0.04 (-0.31, 0.38)	8.39E-01	4.32E-02
M32698	X-11381	0.08 (-0.21, 0.38)	5.81E-01	3.64E-02	0.11 (-0.22, 0.45)	4.96E-01	3.24E-02
M32709	X-03056--N-[3-(2-Oxopyrrolidin-1-yl)propyl]acetamide	-0.09 (-0.37, 0.18)	5.06E-01	3.36E-02	-0.09 (-0.39, 0.22)	5.71E-01	3.48E-02
M32735	X-01911	-0.37 (-0.62, -0.12)	4.58E-03	2.83E-03	-0.43 (-0.71, -0.16)	2.11E-03	8.50E-04
M32739	X-11422--xanthine	-0.31 (-0.66, 0.05)	9.57E-02	1.37E-02	-0.49 (-0.88, -0.11)	1.21E-02	2.97E-03
M32740	X-11423--O-sulfo-L-tyrosine	-0.27 (-0.6, 0.06)	1.06E-01	1.57E-02	-0.19 (-0.54, 0.17)	3.01E-01	2.58E-02
M32753	X-09789	0.02 (-0.27, 0.32)	8.67E-01	4.66E-02	0.13 (-0.17, 0.43)	4.00E-01	2.93E-02
M32755	X-11438	-0.16 (-0.43, 0.12)	2.68E-01	2.42E-02	-0.28 (-0.58, 0.01)	5.89E-02	9.77E-03
M32757	X-11440	0.01 (-0.27, 0.28)	9.53E-01	4.84E-02	0.03 (-0.27, 0.34)	8.23E-01	4.28E-02
M32758	X-11441	-0.12 (-0.45, 0.21)	4.80E-01	3.26E-02	-0.03 (-0.39, 0.33)	8.69E-01	4.41E-02

M32759	X-11442	-0.13 (-0.46, 0.19)	4.19E-01	3.03E-02	-0.09 (-0.45, 0.26)	6.01E-01	3.60E-02
M32761	X-11444	-0.09 (-0.38, 0.21)	5.73E-01	3.61E-02	0.01 (-0.3, 0.33)	9.29E-01	4.63E-02
M32762	X-11445--5-alpha-pregnan-3beta,20alpha-disulfate	-0.17 (-0.44, 0.1)	2.23E-01	2.18E-02	-0.17 (-0.47, 0.14)	2.82E-01	2.45E-02
M32769	X-11452	-0.19 (-0.45, 0.07)	1.47E-01	1.81E-02	-0.22 (-0.51, 0.06)	1.25E-01	1.54E-02
M32786	X-11469	-0.19 (-0.5, 0.13)	2.40E-01	2.27E-02	-0.15 (-0.5, 0.2)	3.96E-01	2.90E-02
M32787	X-11470	-0.13 (-0.41, 0.15)	3.70E-01	2.89E-02	-0.1 (-0.4, 0.2)	5.11E-01	3.30E-02
M32802	X-11485	-0.22 (-0.5, 0.06)	1.26E-01	1.66E-02	-0.29 (-0.61, 0.02)	6.77E-02	1.09E-02
M32814	X-11497	-0.11 (-0.44, 0.22)	5.11E-01	3.39E-02	0.16 (-0.13, 0.46)	2.79E-01	2.41E-02
M32836	HWESASXX*	0.18 (-0.13, 0.5)	2.53E-01	2.34E-02	0.27 (-0.06, 0.6)	1.06E-01	1.35E-02
M32847	X-11530	-0.35 (-0.65, -0.05)	2.23E-02	5.81E-03	-0.32 (-0.65, 0.01)	6.05E-02	9.92E-03
M32854	X-11537	0.04 (-0.26, 0.34)	7.93E-01	4.33E-02	0.19 (-0.1, 0.47)	2.02E-01	2.07E-02
M32855	X-11538	0.06 (-0.22, 0.35)	6.61E-01	3.90E-02	0.17 (-0.14, 0.48)	2.81E-01	2.42E-02
M32857	X-11540	0.02 (-0.29, 0.34)	8.93E-01	4.73E-02	0.11 (-0.19, 0.4)	4.82E-01	3.22E-02
M32867	X-11550	0.21 (-0.11, 0.54)	1.95E-01	2.03E-02	0.41 (0.07, 0.75)	1.95E-02	4.39E-03
M32869	X-11552	0.08 (-0.26, 0.41)	6.58E-01	3.87E-02	0.04 (-0.33, 0.41)	8.17E-01	4.26E-02
M32910	X-11593--O-methylascorbate*	-0.21 (-0.5, 0.08)	1.52E-01	1.83E-02	-0.3 (-0.61, 0)	5.12E-02	8.92E-03
M32980	adrenate (22:4n6)	0.15 (-0.11, 0.41)	2.56E-01	2.37E-02	0.19 (-0.08, 0.46)	1.63E-01	1.84E-02
M33009	homostachydrine*	0.26 (-0.03, 0.55)	8.03E-02	1.29E-02	0.35 (0.04, 0.66)	2.83E-02	5.24E-03
M33084	ADSGEGDFXAEGGGVR*	0.2 (-0.11, 0.52)	1.95E-01	2.01E-02	-0.12 (-0.44, 0.19)	4.36E-01	3.07E-02
M33131	X-11786--methylcysteine	0.02 (-0.28, 0.31)	9.03E-01	4.76E-02	-0.06 (-0.4, 0.27)	7.08E-01	3.99E-02
M33132	X-11787	0.13 (-0.15, 0.41)	3.70E-01	2.90E-02	0.06 (-0.24, 0.36)	6.98E-01	3.97E-02
M33138	X-11793--oxidized bilirubin*	-0.14 (-0.42, 0.13)	3.08E-01	2.63E-02	-0.03 (-0.34, 0.27)	8.24E-01	4.29E-02
M33140	X-11795	0.01 (-0.28, 0.29)	9.68E-01	4.87E-02	0.09 (-0.23, 0.42)	5.71E-01	3.51E-02
M33144	X-11799	0.19 (-0.1, 0.49)	1.96E-01	2.04E-02	0.34 (0.03, 0.65)	3.44E-02	6.09E-03
M33150	X-11805	-0.46 (-0.76, -0.17)	2.43E-03	1.70E-03	-0.53 (-0.86, -0.19)	2.01E-03	7.08E-04
M33154	X-11809	0.33 (0.03, 0.62)	3.02E-02	6.80E-03	0.38 (0.06, 0.7)	1.96E-02	4.53E-03
M33163	X-11818	0.2 (-0.07, 0.47)	1.47E-01	1.80E-02	-0.03 (-0.32, 0.25)	8.06E-01	4.24E-02
M33165	X-11820	0.3 (-0.03, 0.63)	7.29E-02	1.18E-02	0.34 (0.02, 0.65)	3.81E-02	7.37E-03
M33192	X-11847	-0.17 (-0.49, 0.14)	2.74E-01	2.48E-02	-0.25 (-0.6, 0.09)	1.44E-01	1.69E-02
M33194	X-11849	-0.21 (-0.53, 0.11)	2.02E-01	2.11E-02	-0.3 (-0.65, 0.05)	9.37E-02	1.26E-02
M33204	X-11859	-0.06 (-0.4, 0.28)	7.36E-01	4.09E-02	0.19 (-0.15, 0.53)	2.62E-01	2.34E-02
M33225	X-11880	0.02 (-0.28, 0.33)	8.95E-01	4.75E-02	-0.08 (-0.42, 0.25)	6.30E-01	3.77E-02
M33228	1-arachidonoylglycerophosphocholine*	0.27 (-0.02, 0.57)	7.10E-02	1.15E-02	0.29 (-0.02, 0.6)	6.46E-02	1.03E-02
M33230	1-palmitoleoylglycerophosphocholine*	0.28 (-0.01, 0.58)	6.19E-02	1.05E-02	0.31 (0.01, 0.61)	4.38E-02	7.79E-03
M33380	X-12029	-0.12 (-0.42, 0.19)	4.56E-01	3.19E-02	-0.07 (-0.4, 0.26)	6.69E-01	3.88E-02
M33389	X-12038	-0.09 (-0.43, 0.25)	6.00E-01	3.71E-02	-0.08 (-0.37, 0.22)	6.06E-01	3.61E-02
M33390	X-12039	0.38 (0.08, 0.69)	1.37E-02	4.25E-03	0.33 (0.02, 0.64)	3.63E-02	6.66E-03
M33415	X-12063	-0.04 (-0.36, 0.28)	8.14E-01	4.38E-02	-0.21 (-0.53, 0.12)	2.09E-01	2.11E-02
M33422	gamma-glutamylphenylalanine	-0.26 (-0.53, 0.02)	6.63E-02	1.10E-02	-0.3 (-0.59, -0.01)	4.62E-02	7.93E-03
M33441	isobutyrylcarnitine	-0.02 (-0.33, 0.28)	8.75E-01	4.69E-02	-0.01 (-0.34, 0.32)	9.41E-01	4.73E-02
M33442	pseudouridine	-0.22 (-0.52, 0.08)	1.54E-01	1.84E-02	-0.22 (-0.52, 0.09)	1.69E-01	1.88E-02
M33443	valerate	-0.03 (-0.31, 0.25)	8.40E-01	4.50E-02	0.08 (-0.23, 0.39)	5.92E-01	3.57E-02
M33447	palmitoleate (16:1n7)	0.02 (-0.25, 0.3)	8.67E-01	4.67E-02	0 (-0.27, 0.27)	9.83E-01	4.94E-02
M33477	erythronate*	0.13 (-0.16, 0.42)	3.73E-01	2.92E-02	0.07 (-0.24, 0.38)	6.67E-01	3.85E-02
M33507	X-12092	0.19 (-0.09, 0.46)	1.87E-01	1.94E-02	0.21 (-0.1, 0.51)	1.84E-01	1.95E-02
M33509	X-12094	-0.17 (-0.45, 0.1)	2.16E-01	2.14E-02	-0.13 (-0.42, 0.16)	3.90E-01	2.88E-02
M33510	X-12095--N1-methyl-3-pyridone-4-carboxamide	-0.23 (-0.5, 0.05)	1.04E-01	1.53E-02	-0.19 (-0.48, 0.09)	1.86E-01	1.97E-02
M33515	X-12100--hydroxytryptophan*	-0.26 (-0.51, 0)	4.70E-02	8.92E-03	-0.2 (-0.47, 0.07)	1.52E-01	1.71E-02
M33587	eicosenoate (20:1n9 or 11)	0.04 (-0.24, 0.31)	8.05E-01	4.36E-02	-0.04 (-0.32, 0.23)	7.66E-01	4.14E-02
M33627	X-12206	0.03 (-0.26, 0.33)	8.28E-01	4.45E-02	-0.03 (-0.35, 0.29)	8.48E-01	4.35E-02
M33638	X-12217	0.25 (-0.03, 0.54)	8.03E-02	1.27E-02	0.35 (0.02, 0.67)	3.49E-02	6.23E-03
M33653	X-12231	-0.25 (-0.51, 0)	5.02E-02	9.77E-03	-0.26 (-0.54, 0.02)	6.60E-02	1.05E-02

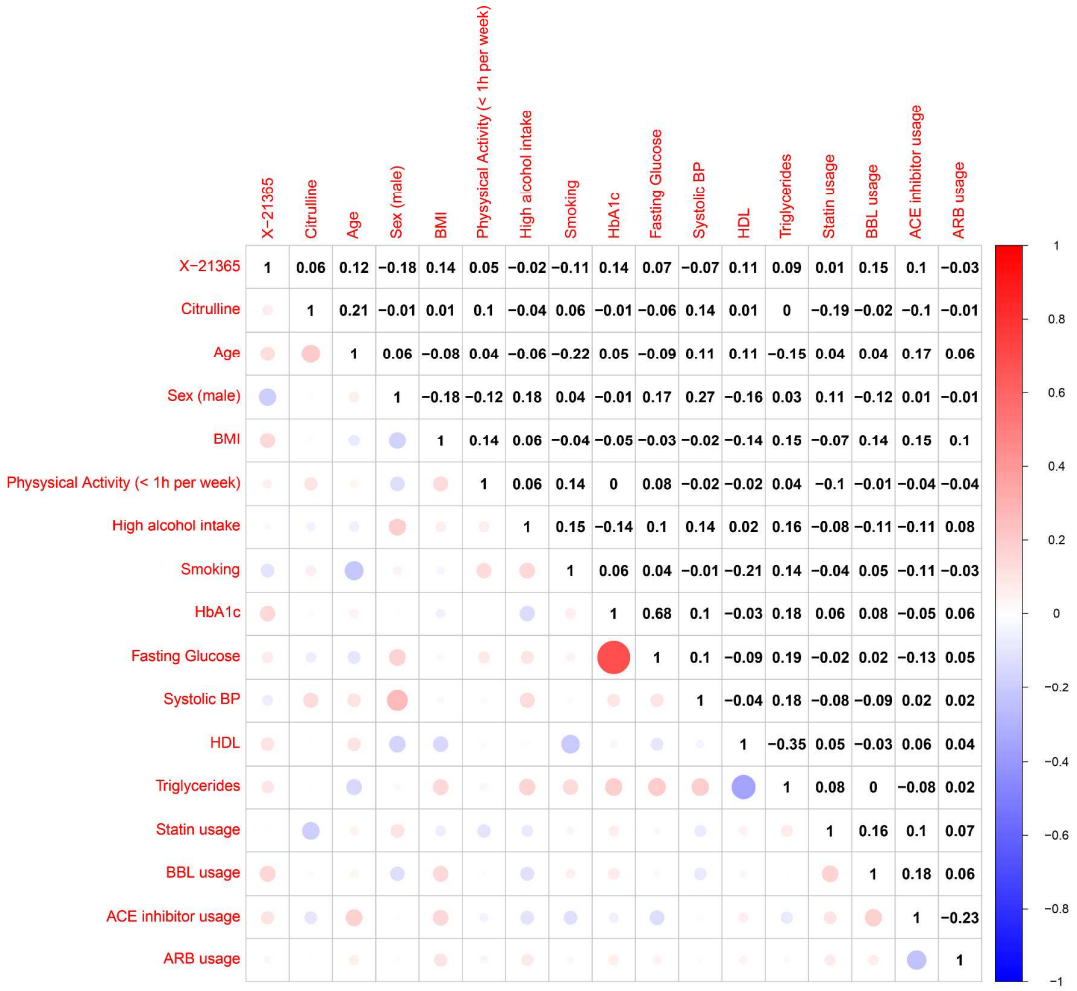
M33666	X-12244--N-acetylcarnosine	-0.45 (-0.73, -0.17)	1.61E-03	1.27E-03	-0.46 (-0.76, -0.16)	3.15E-03	1.27E-03
M33675	X-12253	-0.05 (-0.35, 0.25)	7.34E-01	4.08E-02	-0.01 (-0.33, 0.31)	9.65E-01	4.89E-02
M33801	ADpSGEGDFXAEGGGVR*	0.26 (-0.07, 0.59)	1.25E-01	1.64E-02	0.16 (-0.21, 0.52)	4.07E-01	2.96E-02
M33821	1-eicosatrienoylglycerophosphocholine*	0.24 (-0.02, 0.5)	7.18E-02	1.16E-02	0.17 (-0.11, 0.45)	2.30E-01	2.21E-02
M33822	1-docosahexaenoylglycerophosphocholine*	0.08 (-0.22, 0.38)	5.99E-01	3.70E-02	0.07 (-0.24, 0.38)	6.53E-01	3.82E-02
M33833	X-12405	0.29 (0, 0.57)	4.91E-02	9.49E-03	0.21 (-0.11, 0.54)	1.94E-01	2.01E-02
M33871	1-eicosadienoylglycerophosphocholine*	0.19 (-0.13, 0.52)	2.41E-01	2.28E-02	0.25 (-0.08, 0.58)	1.43E-01	1.66E-02
M33883	X-12441--12-hydroxyeicosatetraenoate (12-HETE)	-0.17 (-0.46, 0.12)	2.44E-01	2.29E-02	-0.3 (-0.62, 0.02)	6.69E-02	1.08E-02
M33884	X-12442--5,8-tetradecadienoate	-0.11 (-0.37, 0.16)	4.23E-01	3.07E-02	-0.08 (-0.37, 0.21)	5.86E-01	3.56E-02
M33935	piperine	-0.32 (-0.57, -0.06)	1.50E-02	4.82E-03	-0.35 (-0.63, -0.06)	1.66E-02	4.11E-03
M33936	octanoylcarnitine	-0.23 (-0.51, 0.05)	1.04E-01	1.54E-02	-0.23 (-0.54, 0.07)	1.34E-01	1.59E-02
M33937	alpha-hydroxyisovalerate	0.06 (-0.22, 0.34)	6.73E-01	3.91E-02	0.08 (-0.22, 0.37)	6.15E-01	3.65E-02
M33941	decanoylcarnitine	-0.14 (-0.42, 0.15)	3.51E-01	2.76E-02	-0.09 (-0.4, 0.22)	5.71E-01	3.50E-02
M33955	1-palmitoylglycerophosphocholine	0.19 (-0.1, 0.48)	1.91E-01	1.97E-02	0.23 (-0.08, 0.54)	1.42E-01	1.64E-02
M33957	1-heptadecanoylglycerophosphocholine	0.2 (-0.11, 0.51)	1.97E-01	2.05E-02	0.3 (-0.03, 0.63)	7.02E-02	1.12E-02
M33960	1-oleoylglycerophosphocholine	0.32 (0.02, 0.63)	3.82E-02	7.51E-03	0.32 (0.01, 0.64)	4.06E-02	7.65E-03
M33961	1-stearoylglycerophosphocholine	0.13 (-0.17, 0.44)	3.85E-01	2.96E-02	0.17 (-0.13, 0.48)	2.64E-01	2.35E-02
M33968	5-dodecenoate (12:1n7)	-0.24 (-0.53, 0.05)	1.01E-01	1.46E-02	-0.25 (-0.55, 0.05)	1.07E-01	1.36E-02
M33969	stearidonate (18:4n3)	-0.01 (-0.28, 0.26)	9.44E-01	4.79E-02	-0.02 (-0.3, 0.26)	9.03E-01	4.55E-02
M33971	10-heptadecenoate (17:1n7)	0.04 (-0.21, 0.3)	7.38E-01	4.12E-02	-0.03 (-0.29, 0.24)	8.45E-01	4.33E-02
M33972	10-nonadecenoate (19:1n9)	0.07 (-0.21, 0.34)	6.40E-01	3.81E-02	-0.05 (-0.33, 0.23)	7.15E-01	4.02E-02
M33973	epiandrosterone sulfate	-0.21 (-0.51, 0.09)	1.69E-01	1.88E-02	-0.2 (-0.54, 0.13)	2.28E-01	2.20E-02
M34035	linolenate [alpha or gamma; (18:3n3 or 6)]	0.17 (-0.13, 0.47)	2.62E-01	2.38E-02	0.18 (-0.12, 0.48)	2.31E-01	2.22E-02
M34040	X-12510--2-aminooctanoic acid	-0.1 (-0.39, 0.18)	4.76E-01	3.22E-02	-0.08 (-0.4, 0.25)	6.44E-01	3.80E-02
M34062	X-12524	0.31 (0.03, 0.59)	3.19E-02	7.08E-03	0.34 (0.04, 0.65)	2.70E-02	4.96E-03
M34106	bilirubin (E,Z or Z,E)*	0.12 (-0.16, 0.39)	4.04E-01	2.97E-02	0.14 (-0.16, 0.45)	3.63E-01	2.76E-02
M34112	X-12544	-0.28 (-0.57, 0.02)	6.55E-02	1.08E-02	-0.2 (-0.53, 0.13)	2.23E-01	2.17E-02
M34123	X-12556	-0.06 (-0.36, 0.24)	6.92E-01	3.97E-02	-0.13 (-0.46, 0.21)	4.50E-01	3.16E-02
M34214	1-arachidonoylglycerophosphoinositol*	0.3 (0, 0.6)	5.09E-02	9.92E-03	0.15 (-0.17, 0.48)	3.57E-01	2.75E-02
M34221	X-12627	-0.11 (-0.43, 0.2)	4.82E-01	3.27E-02	-0.16 (-0.48, 0.17)	3.50E-01	2.72E-02
M34244	X-12644	0.03 (-0.31, 0.37)	8.50E-01	4.56E-02	-0.15 (-0.49, 0.2)	4.13E-01	2.99E-02
M34283	asparagine	0.25 (-0.07, 0.56)	1.27E-01	1.67E-02	0.3 (-0.04, 0.64)	8.46E-02	1.22E-02
M34306	X-12696	-0.08 (-0.39, 0.22)	5.97E-01	3.68E-02	0.13 (-0.2, 0.46)	4.50E-01	3.13E-02
M34359	X-12749	-0.22 (-0.5, 0.06)	1.20E-01	1.63E-02	-0.24 (-0.55, 0.06)	1.19E-01	1.46E-02
M34384	stachydrine	0.07 (-0.23, 0.36)	6.46E-01	3.84E-02	-0.08 (-0.4, 0.24)	6.28E-01	3.74E-02
M34407	isovalerylcarnitine	-0.33 (-0.59, -0.07)	1.46E-02	4.53E-03	-0.32 (-0.61, -0.03)	2.98E-02	5.52E-03
M34409	stearoylcarnitine	-0.07 (-0.36, 0.22)	6.34E-01	3.80E-02	0.01 (-0.28, 0.31)	9.34E-01	4.70E-02
M34416	1-stearoylglycerophosphoethanolamine	-0.08 (-0.41, 0.24)	6.09E-01	3.74E-02	-0.11 (-0.45, 0.23)	5.29E-01	3.37E-02
M34419	1-linoleoylglycerophosphocholine	0.22 (-0.07, 0.52)	1.32E-01	1.70E-02	0.21 (-0.1, 0.52)	1.81E-01	1.93E-02
M34420	bradykinin, des-arg(9)	0.29 (-0.03, 0.6)	7.43E-02	1.19E-02	0.2 (-0.13, 0.54)	2.33E-01	2.24E-02
M34453	X-12776	-0.08 (-0.4, 0.24)	6.13E-01	3.75E-02	0.06 (-0.3, 0.41)	7.54E-01	4.11E-02
M34469	X-12786	-0.07 (-0.36, 0.22)	6.42E-01	3.82E-02	-0.16 (-0.47, 0.15)	3.14E-01	2.62E-02
M34481	X-12798	-0.19 (-0.49, 0.1)	2.00E-01	2.08E-02	-0.1 (-0.43, 0.23)	5.42E-01	3.43E-02
M34527	X-12844	0.04 (-0.31, 0.38)	8.42E-01	4.52E-02	0.24 (-0.14, 0.62)	2.08E-01	2.10E-02
M34534	laurylcarnitine	-0.14 (-0.42, 0.14)	3.12E-01	2.68E-02	-0.13 (-0.43, 0.17)	3.82E-01	2.85E-02
M34674	X-12990--docosapentaenoic acid (n6-DPA)	0.09 (-0.2, 0.38)	5.31E-01	3.48E-02	0.17 (-0.15, 0.49)	2.93E-01	2.52E-02
M34732	isovalerate	-0.03 (-0.34, 0.29)	8.57E-01	4.59E-02	0.02 (-0.33, 0.36)	9.30E-01	4.66E-02
M34761	X-13069	0.19 (-0.08, 0.46)	1.61E-01	1.86E-02	0.16 (-0.13, 0.44)	2.83E-01	2.46E-02
M34878	X-13183--stearamide	-0.04 (-0.33, 0.25)	7.70E-01	4.22E-02	0.01 (-0.3, 0.32)	9.60E-01	4.80E-02
M35072	X-13372	0 (-0.25, 0.26)	9.70E-01	4.89E-02	0.03 (-0.26, 0.32)	8.26E-01	4.31E-02
M35114	7-methylguanine	-0.01 (-0.31, 0.29)	9.48E-01	4.82E-02	0.04 (-0.28, 0.37)	7.90E-01	4.18E-02
M35126	phenylacetylglutamine	0.14 (-0.14, 0.42)	3.29E-01	2.71E-02	0.17 (-0.14, 0.47)	2.82E-01	2.44E-02

M35127	pro-hydroxy-pro	-0.39 (-0.7, -0.08)	1.36E-02	4.11E-03	-0.32 (-0.66, 0.02)	6.60E-02	1.06E-02
M35159	cysteine-glutathione disulfide	0.17 (-0.11, 0.46)	2.35E-01	2.22E-02	0.24 (-0.06, 0.55)	1.19E-01	1.47E-02
M35160	oleoylcarnitine	-0.05 (-0.35, 0.24)	7.17E-01	4.01E-02	0 (-0.31, 0.3)	9.91E-01	4.97E-02
M35186	1-arachidonoylglycerophosphoethanolamine*	0.3 (-0.04, 0.64)	8.18E-02	1.32E-02	0.2 (-0.14, 0.53)	2.47E-01	2.29E-02
M35189	X-13431--nonanoylcarnitine*	-0.32 (-0.6, -0.04)	2.31E-02	6.09E-03	-0.39 (-0.7, -0.08)	1.32E-02	3.40E-03
M35193	X-13435	-0.16 (-0.45, 0.12)	2.64E-01	2.39E-02	-0.05 (-0.37, 0.26)	7.43E-01	4.08E-02
M35240	X-13477	-0.03 (-0.32, 0.25)	8.21E-01	4.41E-02	-0.05 (-0.37, 0.26)	7.44E-01	4.09E-02
M35253	2-palmitoylglycerophosphocholine*	0.18 (-0.11, 0.47)	2.27E-01	2.21E-02	0.21 (-0.08, 0.49)	1.60E-01	1.78E-02
M35254	2-oleoylglycerophosphocholine*	0.17 (-0.12, 0.47)	2.47E-01	2.31E-02	0.12 (-0.18, 0.42)	4.32E-01	3.05E-02
M35255	2-stearoylglycerophosphocholine*	0.18 (-0.15, 0.5)	2.94E-01	2.58E-02	0.21 (-0.11, 0.53)	1.99E-01	2.05E-02
M35257	2-linoleoylglycerophosphocholine*	0.29 (-0.01, 0.58)	5.74E-02	1.02E-02	0.33 (0.03, 0.64)	3.40E-02	5.95E-03
M35270	X-13496	-0.11 (-0.4, 0.19)	4.85E-01	3.30E-02	-0.21 (-0.51, 0.09)	1.74E-01	1.91E-02
M35305	1-palmitoylglycerophosphoinositol*	0.12 (-0.18, 0.42)	4.28E-01	3.12E-02	0.1 (-0.22, 0.43)	5.30E-01	3.39E-02
M35320	catechol sulfate	0.29 (-0.01, 0.6)	6.09E-02	1.03E-02	0.36 (0.02, 0.71)	3.66E-02	6.80E-03
M35326	X-13548	-0.09 (-0.38, 0.21)	5.69E-01	3.60E-02	-0.22 (-0.54, 0.1)	1.73E-01	1.90E-02
M35327	X-13549	-0.16 (-0.49, 0.17)	3.52E-01	2.78E-02	-0.28 (-0.64, 0.08)	1.24E-01	1.53E-02
M35397	X-13619	0.33 (0.01, 0.65)	4.15E-02	7.93E-03	0.22 (-0.13, 0.57)	2.16E-01	2.15E-02
M35431	2-methylbutyroylcarnitine	-0.06 (-0.32, 0.2)	6.53E-01	3.85E-02	-0.12 (-0.41, 0.17)	4.33E-01	3.06E-02
M35433	hydroxyisovaleroyl carnitine	-0.24 (-0.56, 0.08)	1.45E-01	1.78E-02	-0.33 (-0.67, 0.01)	5.55E-02	9.49E-03
M35439	glutaroyl carnitine	-0.51 (-0.8, -0.21)	8.68E-04	9.92E-04	-0.4 (-0.71, -0.08)	1.39E-02	3.82E-03
M35464	X-13671	-0.01 (-0.3, 0.28)	9.57E-01	4.86E-02	0.02 (-0.3, 0.35)	8.82E-01	4.46E-02
M35472	2-tetradecenoyl carnitine	-0.07 (-0.35, 0.2)	5.92E-01	3.65E-02	-0.01 (-0.31, 0.29)	9.43E-01	4.75E-02
M35626	1-myristoylglycerophosphocholine	0.27 (-0.06, 0.6)	1.06E-01	1.56E-02	0.27 (-0.07, 0.61)	1.20E-01	1.49E-02
M35628	1-oleoylglycerophosphoethanolamine	0.41 (0.09, 0.73)	1.13E-02	3.82E-03	0.37 (0.04, 0.7)	2.72E-02	5.10E-03
M35631	1-palmitoylglycerophosphoethanolamine	0.33 (0.03, 0.64)	3.05E-02	6.94E-03	0.38 (0.08, 0.68)	1.35E-02	3.54E-03
M35675	2-hydroxypalmitate	-0.04 (-0.37, 0.28)	7.91E-01	4.32E-02	0.09 (-0.27, 0.45)	6.16E-01	3.67E-02
M35718	dihomo-linolenate (20:3n3 or n6)	0.15 (-0.12, 0.41)	2.74E-01	2.49E-02	0.18 (-0.09, 0.46)	1.91E-01	2.00E-02
M35754	X-13859	-0.05 (-0.37, 0.27)	7.41E-01	4.15E-02	-0.11 (-0.47, 0.24)	5.31E-01	3.40E-02
M35854	threitol	0.36 (0.04, 0.67)	2.68E-02	6.66E-03	0.37 (0.02, 0.71)	3.75E-02	7.22E-03
M35977	X-14056	-0.11 (-0.39, 0.18)	4.49E-01	3.16E-02	-0.08 (-0.39, 0.23)	6.08E-01	3.64E-02
M35978	X-14057	0.01 (-0.3, 0.31)	9.71E-01	4.90E-02	0.02 (-0.31, 0.35)	9.04E-01	4.56E-02
M36009	X-14086	-0.14 (-0.45, 0.17)	3.59E-01	2.82E-02	-0.06 (-0.38, 0.27)	7.39E-01	4.07E-02
M36098	4-vinylphenol sulfate	0.02 (-0.26, 0.3)	8.89E-01	4.72E-02	0.02 (-0.25, 0.29)	8.89E-01	4.48E-02
M36103	p-cresol sulfate	-0.03 (-0.34, 0.27)	8.33E-01	4.49E-02	0.06 (-0.27, 0.39)	7.22E-01	4.04E-02
M36115	X-14189--leucylalanine	-0.45 (-0.76, -0.14)	4.12E-03	2.55E-03	-0.38 (-0.69, -0.08)	1.28E-02	3.12E-03
M36131	X-14205--alpha-glutamyltyrosine	-0.13 (-0.46, 0.2)	4.25E-01	3.09E-02	-0.18 (-0.47, 0.1)	1.97E-01	2.04E-02
M36134	X-14208--phenylalanylserine	-0.26 (-0.65, 0.13)	1.84E-01	1.93E-02	-0.29 (-0.6, 0.03)	7.66E-02	1.15E-02
M36230	X-14304--leucylalanine	-0.41 (-0.71, -0.1)	1.07E-02	3.54E-03	-0.35 (-0.67, -0.04)	2.89E-02	5.38E-03
M36300	X-14374	0.05 (-0.25, 0.36)	7.36E-01	4.11E-02	0.01 (-0.33, 0.35)	9.56E-01	4.79E-02
M36376	X-14450--phenylalanylleucine	-0.53 (-0.86, -0.2)	1.86E-03	1.42E-03	-0.53 (-0.91, -0.15)	6.79E-03	1.84E-03
M36399	X-14473	0.12 (-0.19, 0.43)	4.34E-01	3.14E-02	0.12 (-0.21, 0.44)	4.77E-01	3.20E-02
M36515	X-14588	-0.18 (-0.49, 0.14)	2.69E-01	2.44E-02	-0.08 (-0.42, 0.26)	6.41E-01	3.78E-02
M36552	X-14625	0.4 (0.09, 0.7)	1.07E-02	3.68E-03	0.16 (-0.13, 0.46)	2.74E-01	2.37E-02
M36754	octadecanedioate	0.1 (-0.18, 0.38)	4.95E-01	3.33E-02	0.09 (-0.22, 0.41)	5.60E-01	3.46E-02
M36776	7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	0.1 (-0.23, 0.43)	5.55E-01	3.54E-02	0.19 (-0.16, 0.53)	2.89E-01	2.51E-02
M36808	dimethylarginine (SDMA + ADMA)	-0.06 (-0.42, 0.29)	7.19E-01	4.02E-02	-0.26 (-0.61, 0.09)	1.49E-01	1.70E-02
M36850	taurolithocholate 3-sulfate	0.21 (-0.11, 0.53)	1.94E-01	2.00E-02	0.25 (-0.1, 0.6)	1.62E-01	1.81E-02
M37004	X-14977--vanillin	0 (-0.33, 0.34)	9.84E-01	4.93E-02	0.03 (-0.31, 0.38)	8.49E-01	4.36E-02
M37058	succinylcarnitine	-0.15 (-0.44, 0.15)	3.23E-01	2.69E-02	-0.09 (-0.41, 0.22)	5.59E-01	3.44E-02
M37097	tryptophan betaine	-0.4 (-0.7, -0.11)	6.69E-03	3.26E-03	-0.32 (-0.63, 0)	5.16E-02	9.07E-03
M37190	5alpha-androstan-3beta,17beta-diol disulfate	-0.16 (-0.4, 0.08)	1.91E-01	1.98E-02	-0.17 (-0.43, 0.1)	2.09E-01	2.12E-02
M37202	4-androsten-3beta,17beta-diol disulfate 1*	-0.09 (-0.36, 0.19)	5.43E-01	3.51E-02	-0.13 (-0.42, 0.17)	4.03E-01	2.95E-02

M37203	4-androsten-3beta,17beta-diol disulfate 2*	-0.16 (-0.44, 0.13)	2.84E-01	2.54E-02	-0.17 (-0.49, 0.15)	2.96E-01	2.55E-02
M37506	palmitoyl sphingomyelin	-0.18 (-0.45, 0.09)	1.87E-01	1.95E-02	-0.21 (-0.5, 0.07)	1.42E-01	1.63E-02
M38150	phenylalanylphenylalanine	-0.38 (-0.76, -0.01)	4.56E-02	8.64E-03	-0.45 (-0.8, -0.11)	1.00E-02	2.41E-03
M38178	cis-4-decenoyl carnitine	-0.15 (-0.44, 0.14)	3.05E-01	2.62E-02	-0.04 (-0.36, 0.28)	7.95E-01	4.19E-02
M38768	15-methylpalmitate (isobar with 2-methylpalmitate)	0.04 (-0.26, 0.34)	7.88E-01	4.31E-02	-0.03 (-0.36, 0.3)	8.53E-01	4.38E-02

Crude Model: adjusted for age and sex

Full Model: adjusted for age, sex, body mass index, physical activity, high alcohol intake, smoking status, HbA_{1c}, fasting glucose, high density lipoprotein cholesterol, triglycerides, statin usage, beta blocker usage, angiotensin-converting-enzyme inhibitor usage and angiotensin receptor blocker usage



Supplementary Figure 1. Correlation of citrulline and X-21365 with risk factors of type 2 diabetes

The spearman correlation coefficients between the two metabolites and conventional risk factors of type 2 diabetes including age, sex, body mass index (BMI), physical activity, high alcohol intake (>40g/day in men; >20g/day in women), smoking status, HbA_{1c}, fasting glucose, systolic blood pressure (BP), high density lipoprotein (HDL), triglycerides, statin usage, beta blocker (BBL), Angiotensin converting enzyme usage and angiotensin receptor blocker (ARB) usage in the cross-sectional KORA F4 study are shown for metformin treated type 2 diabetes and non-drug treated type 2 diabetes participants (n=189). Both the size of the circle and intensity of color indicate the degree of correlation between the metabolites and the risk factors. The numeric values of spearman correlation coefficients are shown in the upper triangle.